(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22601 A1

(51) International Patent Classification[7]: C07D 401/14, A61K 31/4427, 31/4155, A61P 35/00, C07D 401/12

(21) International Application Number: PCT/US01/28740

(22) International Filing Date:
14 September 2001 (14.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/232,795	15 September 2000 (15.09.2000)	US
60/257,887	21 December 2000 (21.12.2000)	US
60/286,949	27 April 2001 (27.04.2001)	US

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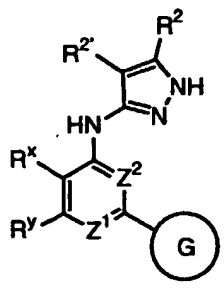
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS



(V)

(57) Abstract: This invention describes novel pyrazole compositions comprising a pharmaceutically acceptable carrier and a compound of formula (V) wherein Z^1 is N, CR^x, or CH, and Z^2 is N or CH, provided one of Z^1 and Z^2 is nitrogen; G is Ring C or Ring D; Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substitutents independently selected from $-R^1$; Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl; R^x and R^y are independently selected from $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form a fused ring; and R^1, R^2, $R^{2'}$, R^3, and T are as described in the specification. The compounds are useful as protein kinase inhibitors, especially as inhibitors of aurora-2 and GSK-3, for treating diseases such as cancer, diabetes and Alzheimer's disease.

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PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to US Provisional Patent Application 60/232,795 filed September 15, 2000, US Provisional Patent Application 60/257,887 filed December 21, 2000 and US Provisional Patent Application 60/286,949 filed April 27, 2001, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is in the field of medicinal chemistry and relates to compounds that are protein kinase inhibitors, compositions containing such compounds and methods of use. More particularly, this invention relates to compounds that are inhibitors of GSK-3 and Aurora-2 protein kinases. The invention also relates to methods of treating diseases associated with these protein kinases, such as diabetes, cancer and Alzheimer's disease.

BACKGROUND OF THE INVENTION

The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of enzymes and other biomolecules associated with target diseases. One important class of enzymes that has been the subject of extensive study is the protein kinases.

Protein kinases mediate intracellular signal transduction. They do this by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There

are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g. osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H_2O_2), cytokines (e.g. interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (e.g. granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF). An extracellular stimulus may effect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis and regulation of cell cycle.

Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease or hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

Aurora-2 is a serine/threonine protein kinase that has been implicated in human cancer, such as colon, breast and other solid tumors. This kinase is believed to be involved in protein phosphorylation events that regulate the cell cycle. Specifically, Aurora-2 may play a role in controlling the accurate segregation of chromosomes during mitosis. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities. In human colon cancer tissue, the aurora-

2 protein has been found to be overexpressed. See Bischoff et al., *EMBO J.*, 1998, 17, 3052-3065; Schumacher et al., *J. Cell Biol.*, 1998, 143, 1635-1646; Kimura et al., *J. Biol. Chem.*, 1997, 272, 13766-13771.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al., *Chemistry & Biology*, 7, 793-803 (2000); Kim and Kimmel, *Curr. Opinion Genetics Dev.*, 10, 508-514 (2000)]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocete hypertrophy [WO 99/65897; WO 00/38675; and Haq et al., *J. Cell Biol.* (2000) 151, 117]. These diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen synthase which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β-catenin, the translation initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-Myc, c-Myb, CREB, and CEPBα. These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated

phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al., *PNAS*, 93, 8455-9 (1996); Cross et al., *Biochem. J.*, 303, 21-26 (1994); Cohen, *Biochem. Soc. Trans.*, 21, 555-567 (1993); Massillon et al., *Biochem J.* 299, 123-128 (1994)]. However, in a diabetic patient where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

GSK-3 activity has also been associated with Alzheimer's disease. This disease is characterized by the well-known β-amyloid peptide and the formation of intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein where Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., *Current Biology* 4, 1077-86 (1994); Brownlees et al., *Neuroreport* 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer's disease.

Another substrate of GSK-3 is β-catenin which is degradated after phosphorylation by GSK-3. Reduced levels of β-catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong et al., *Nature*, 395, 698-702 (1998); Takashima et al., *PNAS*, 90, 7789-93 (1993); Pei et al., *J. Neuropathol. Exp*, 56, 70-78 (1997)].

As a result of the biological importance of GSK-3, there is current interest in therapeutically effective GSK-3 inhbitors. Small molecules that inhibit GSK-3 have recently been reported [WO 99/65897 (Chiron) and WO 00/38675 (SmithKline Beecham)].

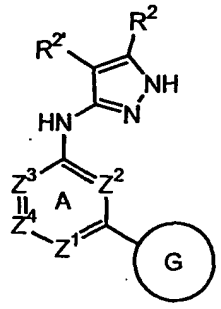
For many of the aforementioned diseases associated with abnormal GSK-3 activity, other protein kinases have also been targeted for treating the same diseases. However, the various protein kinases often act through different biological pathways. For example, certain quinazoline derivatives have been reported recently as inhibitors of p38 kinase (WO 00/12497 to Scios). The compounds are reported to be useful for treating conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity. While p38 activity has been implicated in a wide variety of diseases, including diabetes, p38 kinase is not reported to be a constituent of an insulin signaling pathway that regulates glycogen synthesis or glucose uptake. Therefore, unlike GSK-3, p38 inhibition would not be expected to enhance glycogen synthesis and/or glucose uptake.

There is a continued need to find new therapeutic agents to treat human diseases. The protein kinases aurora-2 and GSK-3 are especially attractive

targets for the discovery of new therapeutics due to their important role in cancer, diabetes, Alzheimer's disease and other diseases.

DESCRIPTION OF THE INVENTION

It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as protein kinase inhibitors, particularly as inhibitors of aurora-2 and GSK-3. These compounds have the general formula I:

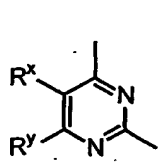


I

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Z^1 to Z^4 are as described below;

Ring A is selected from the group consisting of: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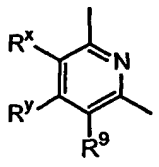
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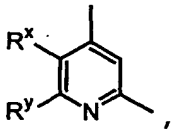
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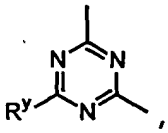
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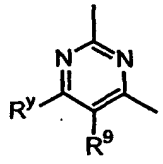

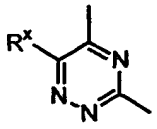

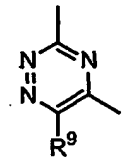

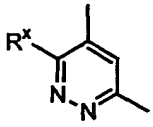

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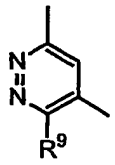


and ;

i

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl,

and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^X and R^Y are independently selected from $T-R^3$, or R^X and R^Y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^X and R^Y is substituted by oxo or $T-R^3$, and any substitutable nitrogen on said ring formed by R^X and R^Y is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, $-T-W-R^6$, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or $-V-R^6$, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

R^3 is selected from -R, -halo, -OR, -C(=O)R, $-CO_2R$, -COCOR, $-COCH_2COR$, $-NO_2$, -CN, -S(O)R, $-S(O)_2R$, -SR, $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, -OC(=O)R, $-N(R^7)COR$, $-N(R^7)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6}

aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, -CO-, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together

with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$; and

R^9 is selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$.

As used herein, the following definitions shall apply unless otherwise indicated. The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted" or with the term "(un)substituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "aliphatic" as used herein means straight-chain, branched or cyclic C_1-C_{12} hydrocarbons which are completely saturated or which contain one or more units of unsaturation but which are not aromatic. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or

(cycloalkyl)alkenyl. The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms. The term "cycloalkyl" used alone or as part of a larger moiety shall include cyclic C_3-C_{12} hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic.

The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

The terms "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" as used herein means an aliphatic ring system having three to fourteen members. The terms "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted. The terms "carbocycle", "carbocyclyl", "carbocyclo", or

"carbocyclic" also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as in a decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to aromatic ring groups having five to fourteen members, such as phenyl, benzyl, phenethyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. The term "aryl" also refers to rings that are optionally substituted. The term "aryl" may be used interchangeably with the term "aryl ring". "Aryl" also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein includes non-aromatic ring systems having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-

morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl. Also included within the scope of the term "heterocyclyl" or "heterocyclic", as it is used herein, is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocycle", "heterocyclyl", or "heterocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted.

The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to heteroaromatic ring groups having five to fourteen members. Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl,

isoindolyl, acridinyl, or benzoisoxazolyl. Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroatomic ring is fused to one or more aromatic or nonaromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[3,4-d]pyrimidinyl. The term "heteroaryl" also refers to rings that are optionally substituted. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Examples of suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group include a halogen, $-R^\circ$, $-OR^\circ$, $-SR^\circ$, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), substituted Ph, $-O(Ph)$, substituted $-O(Ph)$, $-CH_2(Ph)$, substituted $-CH_2(Ph)$, $-CH_2CH_2(Ph)$, substituted $-CH_2CH_2(Ph)$, $-NO_2$, $-CN$, $-N(R^\circ)_2$, $-NR^\circ C(O)R^\circ$, $-NR^\circ C(O)N(R^\circ)_2$, $-NR^\circ CO_2R^\circ$, $-NR^\circ NR^\circ C(O)R^\circ$, $-NR^\circ NR^\circ C(O)N(R^\circ)_2$, $-NR^\circ NR^\circ CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R^\circ)_2$, $-S(O)R^\circ$, $-NR^\circ SO_2N(R^\circ)_2$, $-NR^\circ SO_2R^\circ$, $-C(=S)N(R^\circ)_2$, $-C(=NH)-N(R^\circ)_2$, $-(CH_2)_yNHC(O)R^\circ$, $-(CH_2)_yNHC(O)CH(V-R^\circ)(R^\circ)$; wherein R° is hydrogen, a substituted or unsubstituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, $-O(Ph)$, substituted $-O(Ph)$, $-CH_2(Ph)$, or substituted $-CH_2(Ph)$; y is 0-6; and V is a linker group. Examples of substituents on the aliphatic

group or the phenyl ring of R° include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring include those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, =N-, $=NNHC(O)R^*$, $=NNHCO_2(alkyl)$, $=NNHSO_2(alkyl)$, or $=NR^*$, where each R^* is independently selected from hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group. Examples of substituents on the aliphatic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

Suitable substituents on the nitrogen of a non-aromatic heterocyclic ring include $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, and $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an aliphatic group, a substituted aliphatic group, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), $CH_2(Ph)$, substituted $CH_2(Ph)$, or an unsubstituted heteroaryl or heterocyclic ring. Examples of substituents on the aliphatic group or the phenyl ring include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl,

dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

The term "linker group" or "linker" means an organic moiety that connects two parts of a compound. Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as -NH-, $-CH_2-$, -C(O)-, -C(O)NH-, or a chain of atoms, such as an alkylidene chain. The molecular mass of a linker is typically in the range of about 14 to 200, preferably in the range of 14 to 96 with a length of up to about six atoms. Examples of linkers include a saturated or unsaturated C_{1-6} alkylidene chain which is optionally substituted, and wherein one or two saturated carbons of the chain are optionally replaced by -C(O)-, -C(O)C(O)-, -CONH-, -CONHNH-, $-CO_2-$, -OC(O)-, $-NHCO_2-$, -O-, -NHCONH-, -OC(O)NH-, -NHNH-, -NHCO-, -S-, -SO-, $-SO_2-$, -NH-, $-SO_2NH-$, or $-NHSO_2-$.

The term "alkylidene chain" refers to an optionally substituted, straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation. The optional substituents are as described above for an aliphatic group.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms

of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

Compounds of formula I or salts thereof may be formulated into compositions. In a preferred embodiment, the composition is a pharmaceutical composition. In one embodiment, the composition comprises an amount of the protein kinase inhibitor effective to inhibit a protein kinase, particularly GSK-3, in a biological sample or in a patient. In another embodiment, compounds of this invention and pharmaceutical compositions thereof, which comprise an amount of the protein kinase inhibitor effective to treat or prevent a GSK-3-mediated condition and a pharmaceutically acceptable carrier, adjuvant, or vehicle, may be formulated for administration to a patient.

The term "GSK-3-mediated condition" or "disease", as used herein, means any disease or other deleterious condition or state in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, diabetes, Alzheimer's disease, Huntington's Disease, Parkinson's Disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML),

multiple sclerosis (MS), schizophrenia, cardiomycete hypertrophy, reperfusion/ischemia, and baldness.

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof. This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease. Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia.

Another aspect of the invention relates to inhibiting GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a GSK-3 inhibitor of formula I.

Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease with an Aurora-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "Aurora-2-mediated condition" or "disease", as used herein, means any disease or other

deleterious condition in which Aurora is known to play a role. The term "Aurora-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with an Aurora-2 inhibitor. Such conditions include, without limitation, cancer. The term "cancer" includes, but is not limited to the following cancers: colon and ovarian.

Another aspect of the invention relates to inhibiting Aurora-2 activity in a biological sample, which method comprises contacting the biological sample with the Aurora-2 inhibitor of formula I, or a composition thereof.

Another aspect of this invention relates to a method of treating or preventing a CDK-2-mediated diseases with a CDK-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "CDK-2-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which CDK-2 is known to play a role. The term "CDK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a CDK-2 inhibitor. Such conditions include, without limitation, cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis. See Fischer, P.M. and Lane, D.P., *Current Medicinal Chemistry*, 7, 1213-1245 (2000); Mani, S., Wang, C., Wu, K., Francis, R. and Pestell, R., *Exp. Opin. Invest. Drugs*, 9, 1849 (2000); Fry, D.W. and Garrett, M.D., *Current Opinion in*

Oncologic, Endocrine & Metabolic Investigational Drugs, 2, 40-59 (2000).

Another aspect of the invention relates to inhibiting CDK-2 activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing an ERK-2-mediated diseases with an ERK-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "ERK-mediated condition", as used herein means any disease state or other deleterious condition in which ERK is known to play a role. The term "ERK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ERK-2 inhibitor. Such conditions include, without limitation, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases. The term "cancer" includes, but is not limited to the following cancers: breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma,

papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. ERK-2 protein kinase and its implication in various diseases has been described [Bokemeyer et al. 1996, *Kidney Int.* 49, 1187; Anderson et al., 1990, *Nature* 343, 651; Crews et al., 1992, *Science* 258, 478; Bjorbaek et al., 1995, *J. Biol. Chem.* 270, 18848; Rouse et al., 1994, *Cell* 78, 1027; Raingeaud et al., 1996, *Mol. Cell Biol.* 16, 1247; Raingeaud et al. 1996; Chen et al., 1993 *Proc. Natl. Acad. Sci. USA* 90, 10952; Oliver et al., 1995, *Proc. Soc. Exp. Biol. Med.* 210, 162; Moodie et al., 1993, *Science* 260, 1658; Frey and Mulder, 1997, *Cancer Res.* 57, 628; Sivaraman et al., 1997, *J Clin. Invest.* 99, 1478; Whelchel et al., 1997, *Am. J. Respir. Cell Mol. Biol.* 16, 589].

Another aspect of the invention relates to inhibiting ERK-2 activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing an AKT-mediated diseases with an AKT inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "AKT-mediated condition", as used herein, means any disease state or other deleterious condition in which AKT is known to play a role. The term

"AKT-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a AKT inhibitor. AKT-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, and neurodegenerative disorders. The association of AKT, also known as protein kinase B, with various diseases has been described [Khwaja, A., *Nature*, pp. 33-34, 1990; Zang, Q. Y., et al, *Oncogene*, 19 2000; Kazuhiko, N., et al, *The Journal of Neuroscience*, 20 2000].

Another aspect of the invention relates to inhibiting AKT activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing a Src-mediated disease with a Src inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "Src-mediated condition", as used herein means any disease state or other deleterious condition in which Src is known to play a role. The term "Src-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a Src inhibitor. Such conditions include, without limitation, hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease. Src protein kinase and its implication in various diseases has been described [Soriano, *Cell*, 69, 551 (1992); Soriano et al., *Cell*, 64, 693 (1991); Takayanagi, *J. Clin. Invest.*, 104, 137 (1999); Boschelli,

Drugs of the Future 2000, 25(7), 717, (2000); Talamonti, *J. Clin. Invest.*, 91, 53 (1993); Lutz, *Biochem. Biophys. Res.* 243, 503 (1998); Rosen, *J. Biol. Chem.*, 261, 13754 (1986); Bolen, *Proc. Natl. Acad. Sci. USA*, 84, 2251 (1987); Masaki, *Hepatology*, 27, 1257 (1998); Biscardi, *Adv. Cancer Res.*, 76, 61 (1999); Lynch, *Leukemia*, 7, 1416 (1993); Wiener, *Clin. Cancer Res.*, 5, 2164 (1999); Staley, *Cell Growth Diff.*, 8, 269 (1997)].

Another aspect of the invention relates to inhibiting Src activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "patient" includes human and veterinary subjects.

The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; preparations of an enzyme suitable for *in vitro* assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

The amount effective to inhibit protein kinase, for example, GSK-3 and Aurora-2, is one that measurably inhibits the kinase activity where compared to the activity of the enzyme in the absence of an inhibitor. Any method may be used to determine inhibition, such as,

for example, the Biological Testing Examples described below.

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable

solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When

aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or

cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

In addition to the compounds of this invention, pharmaceutically acceptable derivatives or prodrugs of the compounds of this invention may also be employed in compositions to treat or prevent the above-identified diseases or disorders.

A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or

indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable prodrugs of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in

obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The amount of the protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of the inhibitor will also depend upon the particular compound in the composition.

Depending upon the particular protein kinase-mediated condition to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, in the treatment of diabetes other anti-diabetic

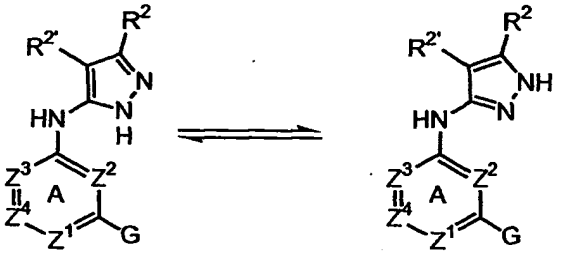
agents may be combined with the GSK-3 inhibitors of this invention to treat diabetes. These agents include, without limitation, insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas.

Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, chemotherapeutic agents or other anti-proliferative agents such as adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

Those additional agents may be administered separately from the protein kinase inhibitor-containing composition, as part of a multiple dosage regimen.

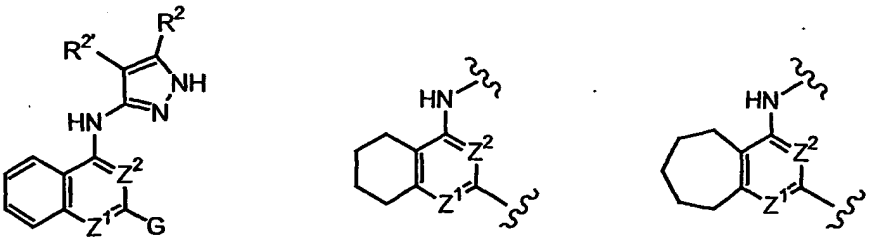
Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor of this invention in a single composition.

Compounds of this invention may exist in alternative tautomeric forms, as in tautomers 1 and 2 shown below. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

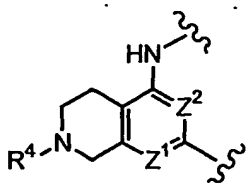


1 2

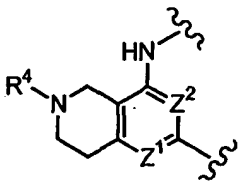
R^x and R^y (at positions Z^3 and Z^4, respectively) may be taken together to form a fused ring, providing a bicyclic ring system containing Ring A. Preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 0-2 heteroatoms, wherein said R^x/R^y ring is optionally substituted. Examples of Ring A systems are shown below by compounds I-A through I-DD, wherein Z^1 is nitrogen or $C(R^9)$ and Z^2 is nitrogen or C(H).



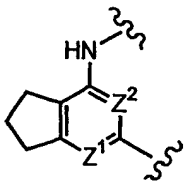
I-A I-B I-C



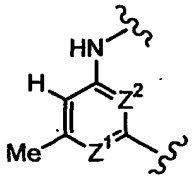
I-D



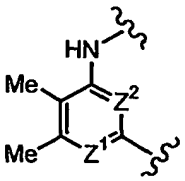
I-E



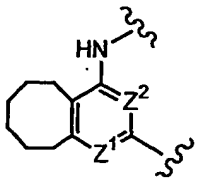
I-F



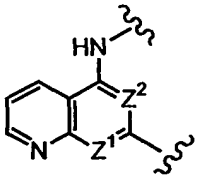
I-G



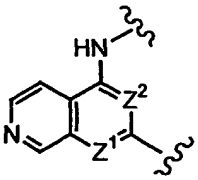
I-H



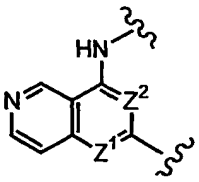
I-I



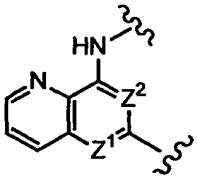
I-J



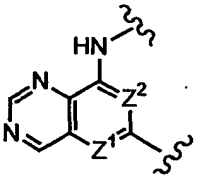
I-K



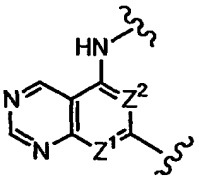
I-L



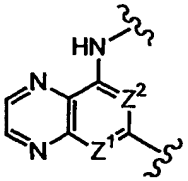
I-M



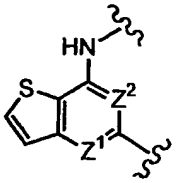
I-N



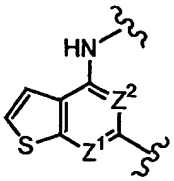
I-O



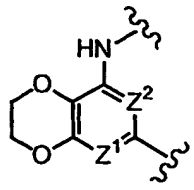
I-P



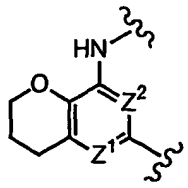
I-Q



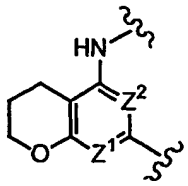
I-R



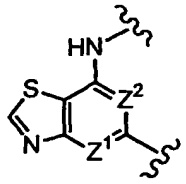
I-S



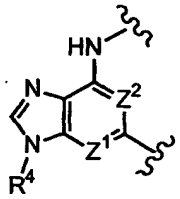
I-T



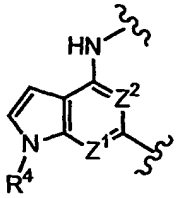
I-U



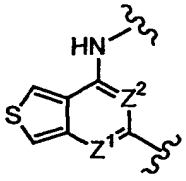
I-V



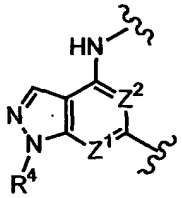
I-W



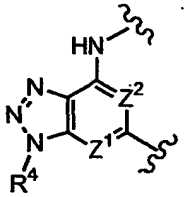
I-X



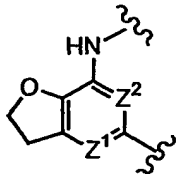
I-Y



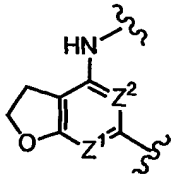
I-Z



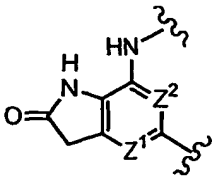
I-AA



I-BB



I-CC



I-DD

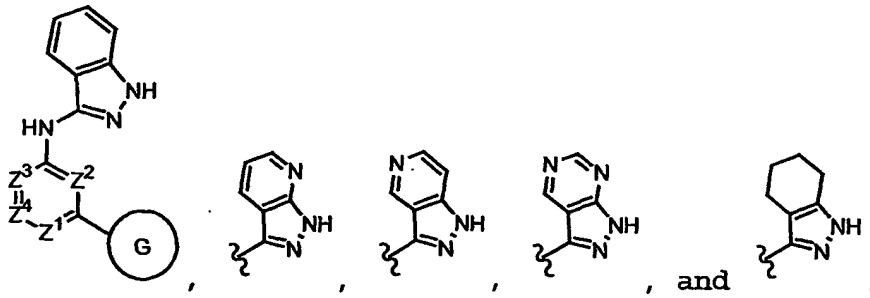
Preferred bicyclic Ring A systems include I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H, I-I, I-J, I-K, I-L, and I-M, more preferably I-A, I-B, I-C, I-F, and I-H, and most preferably I-A, I-B, and I-H.

In the monocyclic Ring A system, preferred R^x groups, when present, include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups, when present, include T-R^3 wherein T is a valence bond or a methylene, and R^3 is -R, -$N(R^4)_2$,

or -OR. Examples of preferred R^Y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl, and methoxymethyl.

In the bicyclic Ring A system, the ring formed when R^X and R^Y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, $-CO_2R$, -COCOR, $-NO_2$, -CN, -S(O)R, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, wherein R and R^4 are as defined above. Preferred R^X/R^Y ring substituents include -halo, -R, -OR, -COR, $-CO_2R$, $-CON(R^4)_2$, -CN, or $-N(R^4)_2$ wherein R is hydrogen or an optionally substituted C_{1-6} aliphatic group.

R^2 and $R^{2'}$ may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring, wherein said fused ring is optionally substituted. These are exemplified in the following formula I compounds having a pyrazole-containing bicyclic ring system:

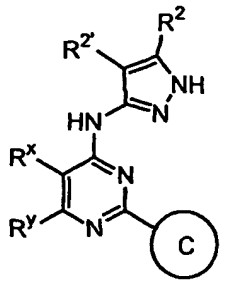


, , , , and .

Preferred substituents on the $R^2/R^{2'}$ fused ring include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-3}$ alkyl, $-C_{1-3}$ haloalkyl, $-NO_2$, $-O(C_{1-3}$ alkyl), $-CO_2(C_{1-3}$ alkyl), -CN, $-SO_2(C_{1-3}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-3}$ alkyl), $-NHC(O)(C_{1-3}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-3}$ alkyl), wherein the (C_{1-3} alkyl) is most preferably methyl.

When the pyrazole ring system is monocyclic, preferred R^2 groups include hydrogen, C_{1-4} aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R^2 substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO_2H, CO_2CH_3, CH_2OH, CH_2OCH_3, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_2Ph$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHCOOC(CH_3)_3$, $CONHCH(CH_3)_2$, $CONHCH_2CH{=}CH_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2Ph$, CONH(cyclohexyl), $CON(Et)_2$, $CON(CH_3)CH_2Ph$, $CONH(n\text{-}C_3H_7)$, $CON(Et)CH_2CH_2CH_3$, $CONHCH_2CH(CH_3)_2$, $CON(n\text{-}C_3H_7)_2$, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), $CONHCH_3$, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), $CONHCH_2CH_2OH$, $CONH_2$, and CO(piperidin-1-yl). A preferred $R^{2'}$ group is hydrogen.

An embodiment that is particularly useful for treating GSK3-mediated diseases relates to compounds of formula II:



II

or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from T-R^3, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8

membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R^3, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, -T-W-R^6, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or -V-R^6, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

R^3 is selected from -R, -halo, -OR, -C(=O)R, $-CO_2R$, -COCOR, $-COCH_2COR$, $-NO_2$, -CN, -S(O)R, $-S(O)_2R$, -SR, $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, $-OC(=O)R$, $-N(R^7)COR$, $-N(R^7)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, -CO-, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

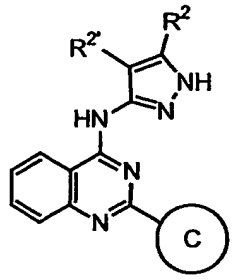
W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

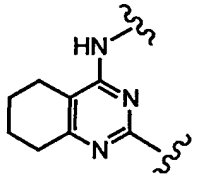
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$.

When the R^x and R^y groups of formula II are taken together to form a fused ring, preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 0-2 heteroatoms, wherein said R^x/R^y ring is optionally substituted. This provides a bicyclic ring system containing a pyrimidine ring. Examples of preferred pyrimidine ring systems of formula II are the mono- and bicyclic systems shown below.



II-A



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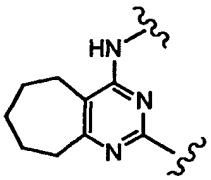

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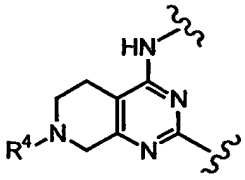

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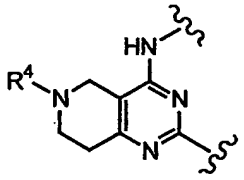

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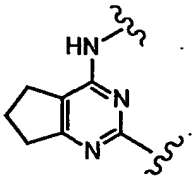

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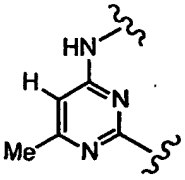

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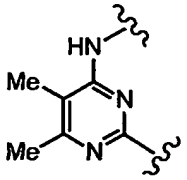

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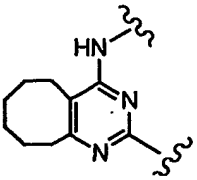

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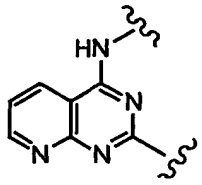

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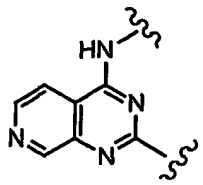

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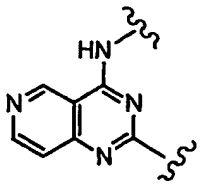

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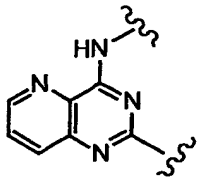

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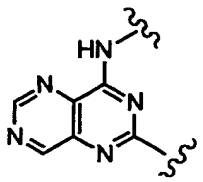

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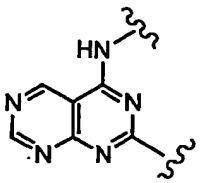

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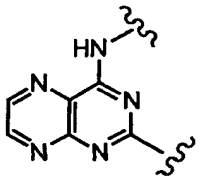


II-P

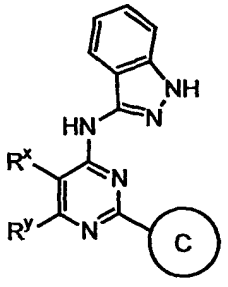
More preferred pyrimidine ring systems of formula II include II-A, II-B, II-C, II-F, and II-H, most preferably II-A, II-B, and II-H.

In the monocyclic pyrimidine ring system of formula II, preferred R^x groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups include $T\text{-}R^3$ wherein T is a valence bond or a methylene, and R^3 is -R, $-N(R^4)_2$, or -OR. When R^3 is -R or -OR, a preferred R is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl

such as phenyl or halo-substituted phenyl, and methoxymethyl.

In the bicyclic pyrimidine ring system of formula II, the ring formed when R^x and R^y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, $-CO_2R$, -COCOR, $-NO_2$, -CN, -S(O)R, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, wherein R and R^4 are as defined above. Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, $-CO_2R$, $-CON(R^4)_2$, -CN, or $-N(R^4)_2$ wherein R is an optionally substituted C_{1-6} aliphatic group.

The R^2 and $R^{2'}$ groups of formula II may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula II compounds having a pyrazole-containing bicyclic ring system:



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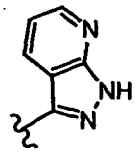

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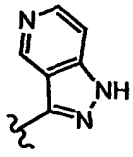

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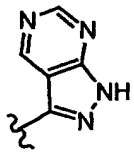

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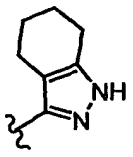

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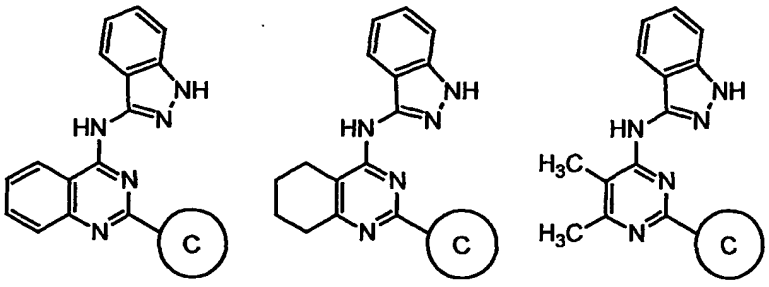
Preferred substituents on the $R^2/R^{2'}$ fused ring of formula II include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$,

-OC(O)NH_2, -NH_2SO_2(C_{1-4} alkyl), -NHC(O)(C_{1-4} alkyl), -C(O)NH_2, and -CO(C_{1-4} alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

When the pyrazole ring system of formula II is monocyclic, preferred R^2 groups include hydrogen, a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group. Examples of such preferred R^2 groups include methyl, t-butyl, -CH_2OCH_3, cyclopropyl, furanyl, thienyl, and phenyl. A preferred $R^{2'}$ group is hydrogen.

More preferred ring systems of formula II are the following, which may be substituted as described above, wherein R^2 and $R^{2'}$ are taken together with the pyrazole ring to form an indazole ring; and R^x and R^y are each methyl, or R^x and R^y are taken together with the pyrimidine ring to form a quinazoline or tetrahydroquinazoline ring:



II-Aa **II-Ba** **II-Ha**

Particularly preferred are those compounds of formula **II-Aa**, **II-Ba**, or **II-Ha** wherein ring C is a phenyl ring and R^1 is halo, methyl, or trifluoromethyl.

Preferred formula II Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is

contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl, quinolinyl and isoquinolinyl.

An important feature of the formula II compounds is the R^1 ortho substituent on Ring C. An ortho position on Ring C or Ring D is defined relative to the position where Ring A is attached. Preferred R^1 groups include -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-CF_3$, -Cl, -F, -CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, $-C\equiv CH$, $-C\equiv C-CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-N(CH_3)_2$, $-CO_2CH_3$, $-CONH_2$, $-NHCOCH_3$, $-OC(O)NH_2$, $-NHSO_2CH_3$, and $-OCF_3$.

On Ring C of formula II, preferred R^5 substituents, when present, include -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, $-C(O)R$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, and $-N(R^4)SO_2R$. More preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic). Examples of such preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, -NHMe, $-NMe_2$, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and $-CO_2Et$.

Preferred formula II compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

(b) R^x is hydrogen or C_{1-4} aliphatic and R^y is $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens;

(c) R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; and

(d) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula II have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(b) R^x is hydrogen or methyl and R^y is -R, $N(R^4)_2$, or -OR, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or partially unsaturated carbocyclo ring optionally substituted with -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$,

$-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$;

(c) R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or -CN;

(d) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(e) each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, $-C(O)R$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R$.

Even more preferred compounds of formula II have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl ring optionally substituted by $-R^5$;

(b) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially unsaturated 6-membered carbocyclo ring;

(c) R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, or -CN;

(d) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring

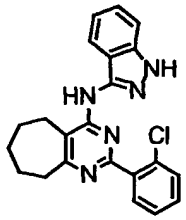
optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

(e) each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic)$_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

Representative compounds of formula II are shown below in Table 1.

Table 1.

II-1



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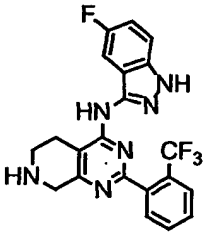

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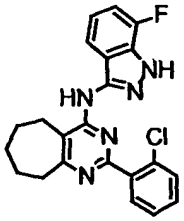

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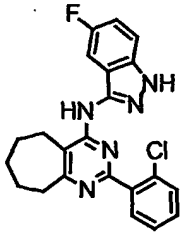

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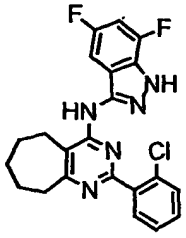

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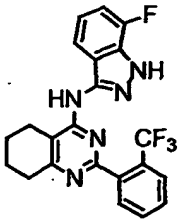

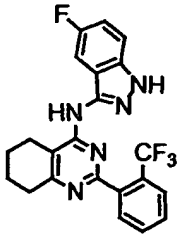

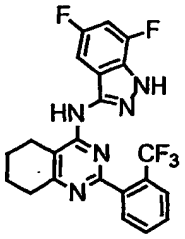

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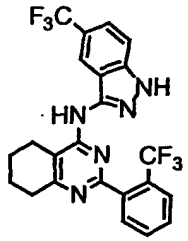

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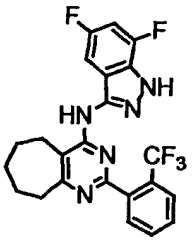

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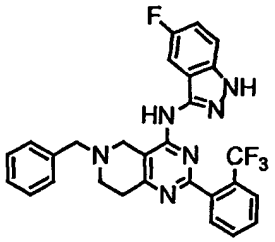

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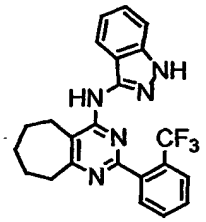

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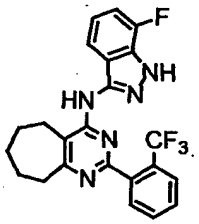

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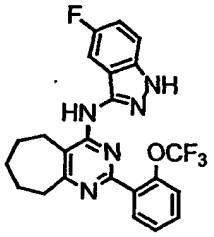

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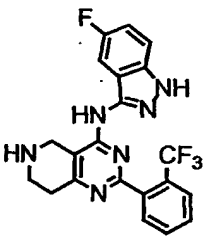

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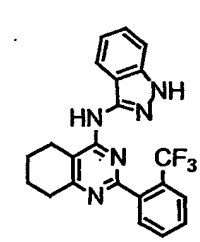

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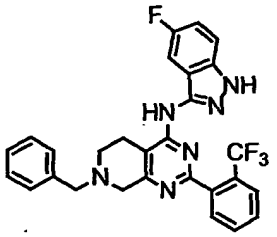

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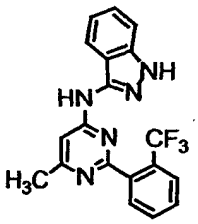

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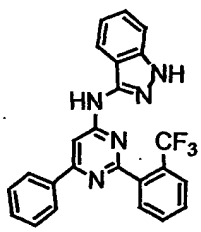

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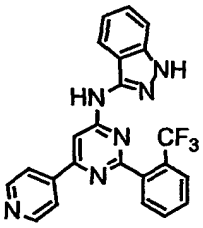

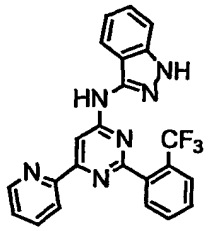

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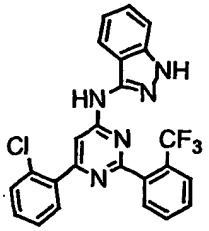

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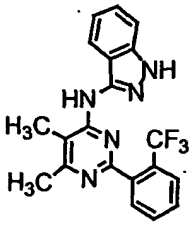

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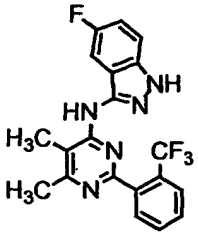

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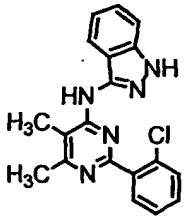

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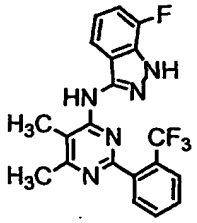

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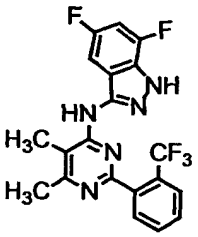

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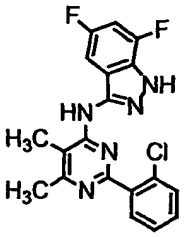

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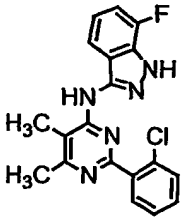

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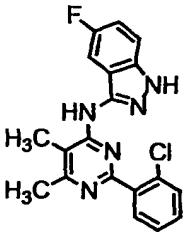

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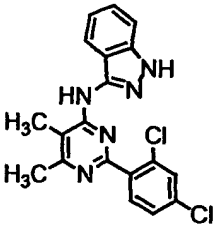

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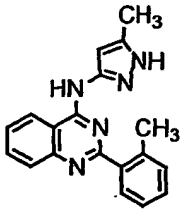

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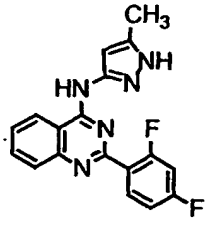

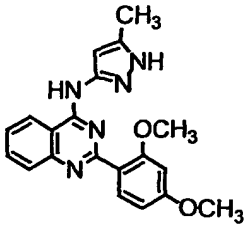

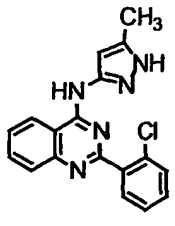

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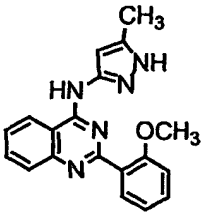

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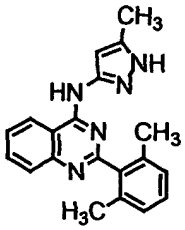

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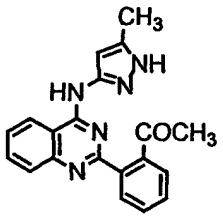

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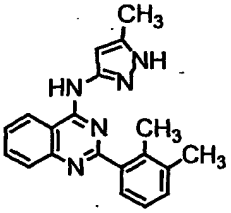

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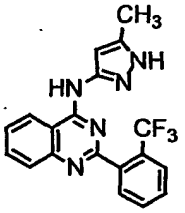

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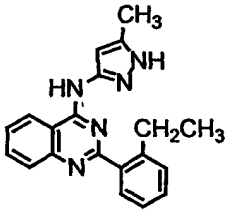

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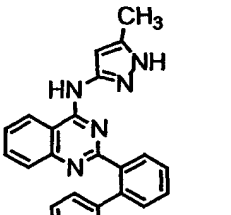

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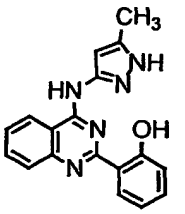

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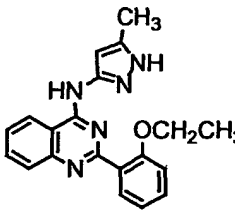

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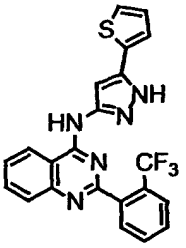

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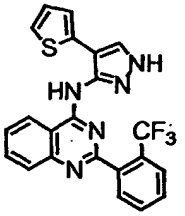

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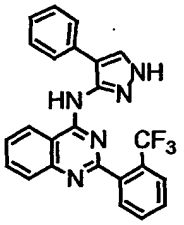

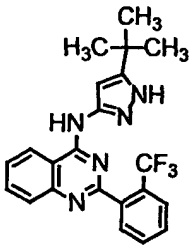

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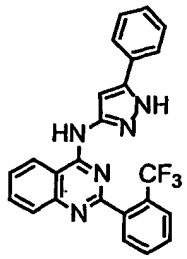

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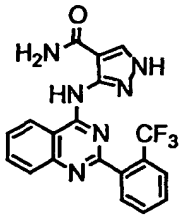
II-51



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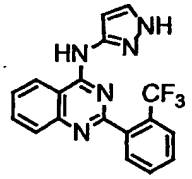

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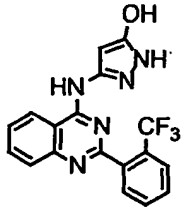

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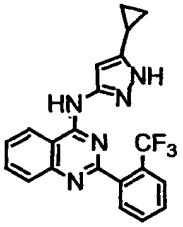

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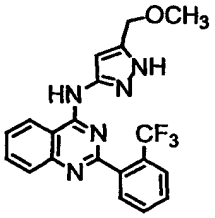

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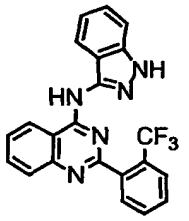

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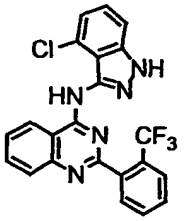

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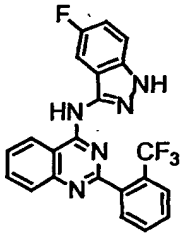

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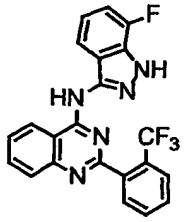

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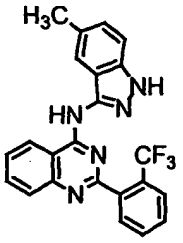

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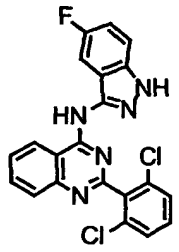

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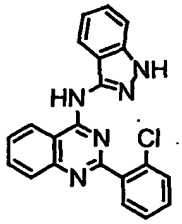

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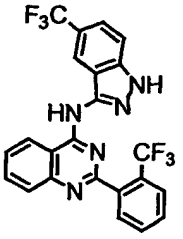

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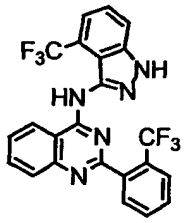

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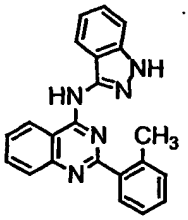
II-66



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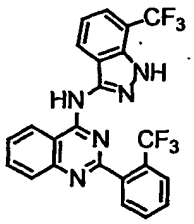

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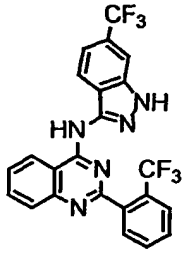

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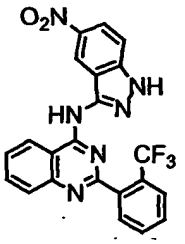

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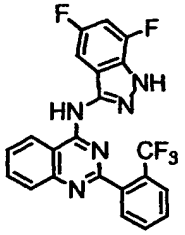

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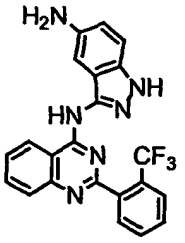

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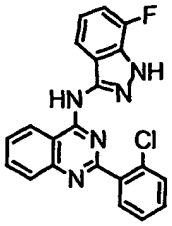

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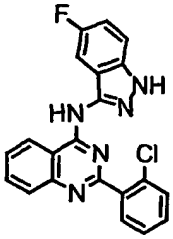

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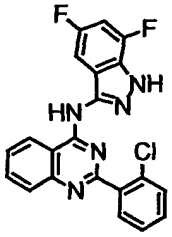

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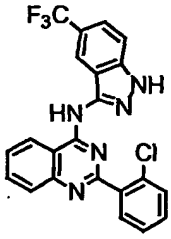

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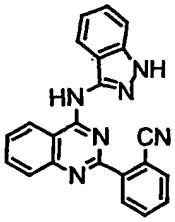

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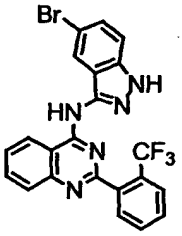

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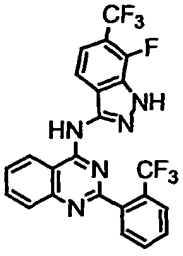

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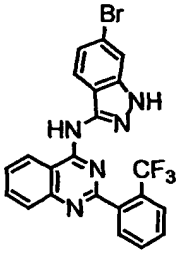

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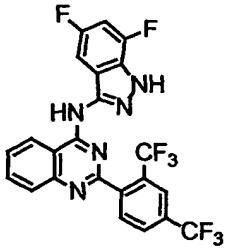

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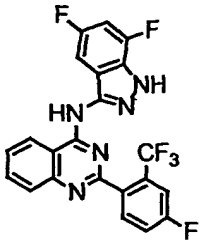

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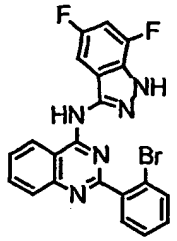

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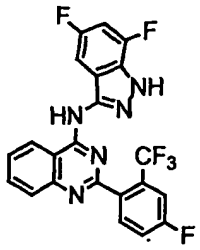

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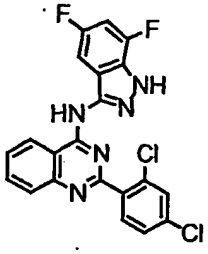

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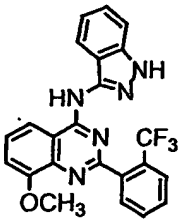

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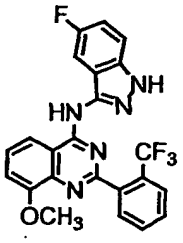

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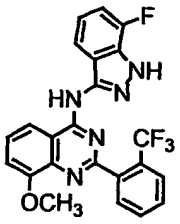

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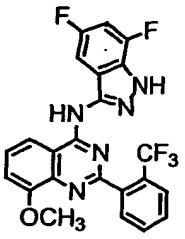

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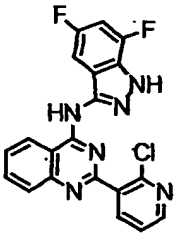

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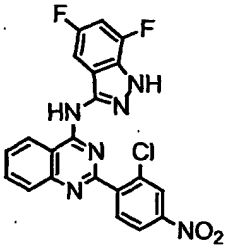

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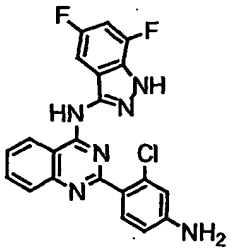

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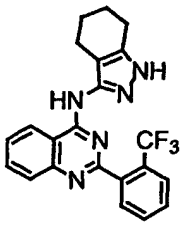

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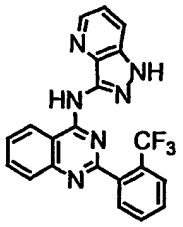

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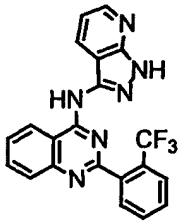

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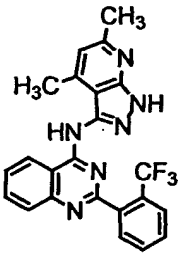

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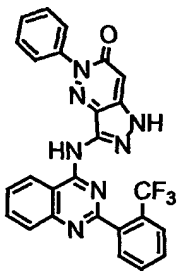

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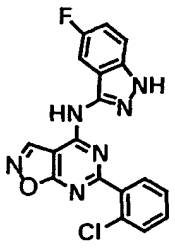

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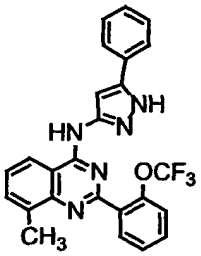

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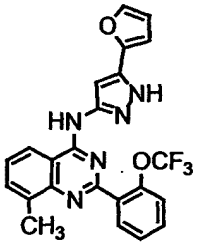

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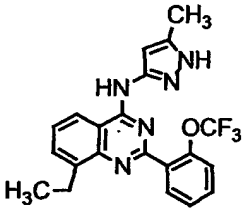

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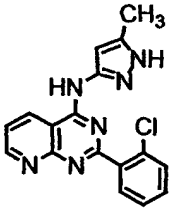

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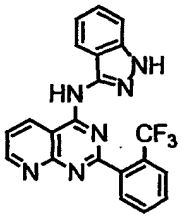
II-107



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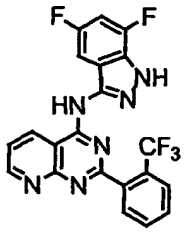

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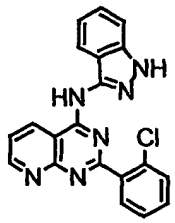

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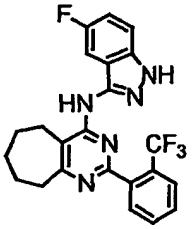

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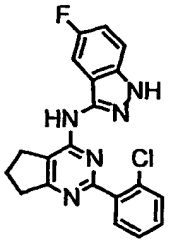

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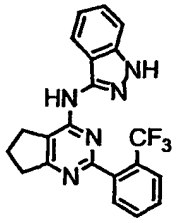

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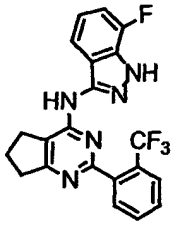

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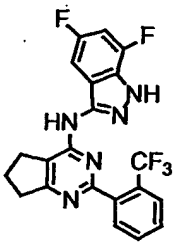

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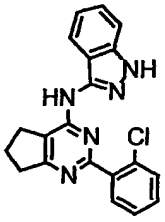

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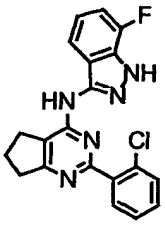

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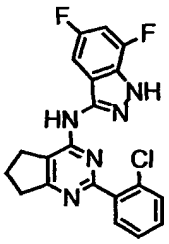

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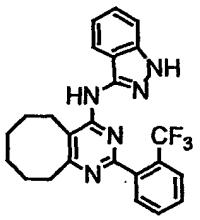

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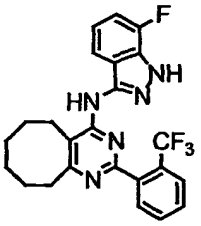

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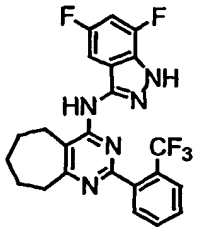

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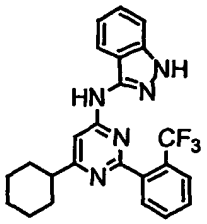

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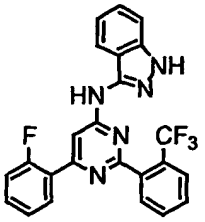

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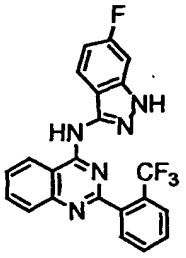

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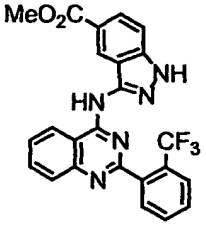

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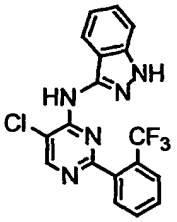

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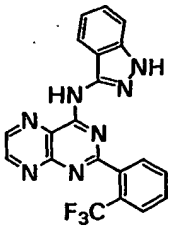

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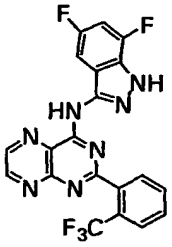

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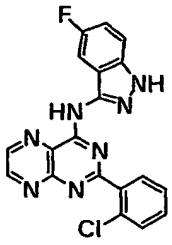

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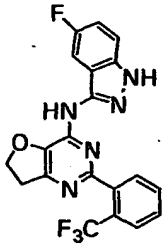

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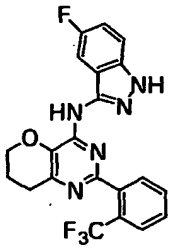

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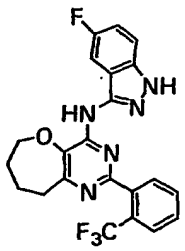

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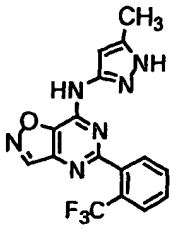

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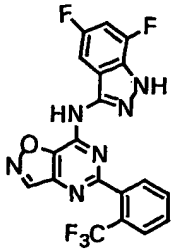

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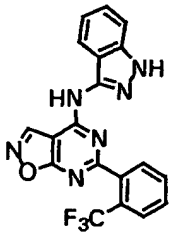

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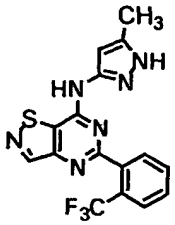

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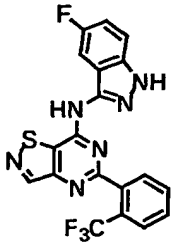

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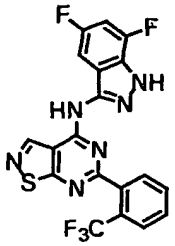

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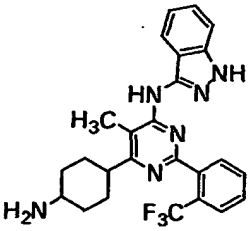

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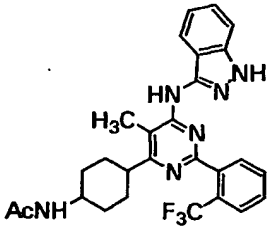

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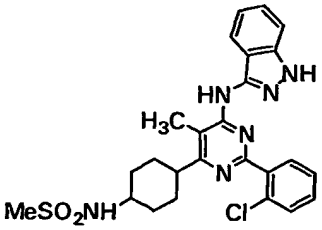

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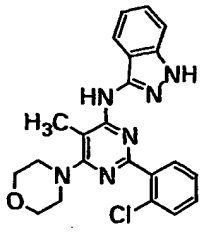

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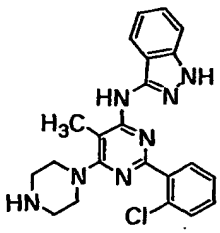

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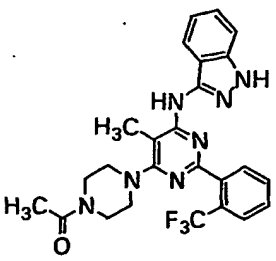

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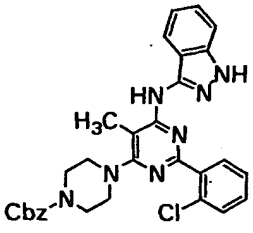

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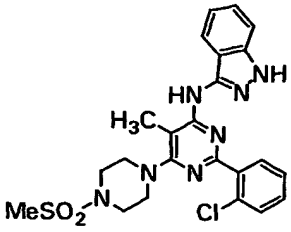

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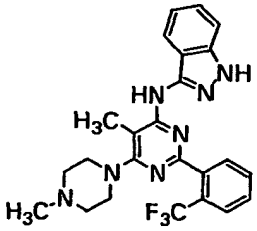

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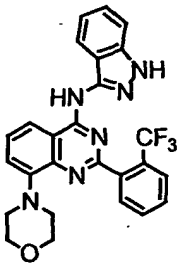

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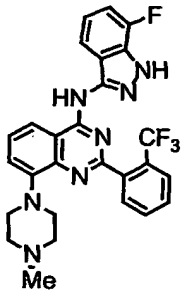

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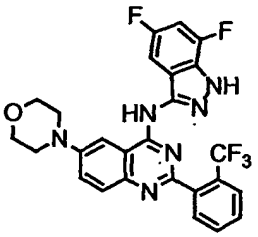

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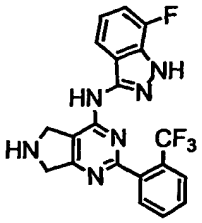

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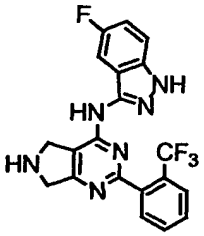

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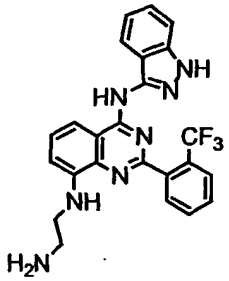

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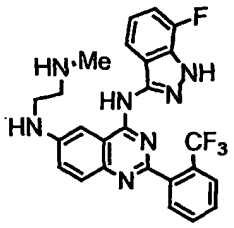

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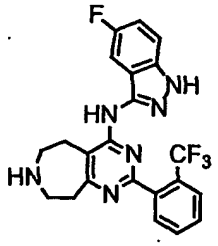

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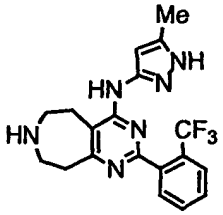

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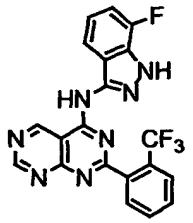

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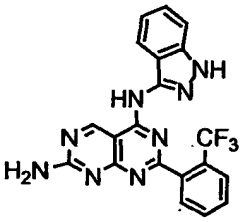

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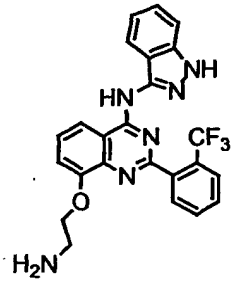

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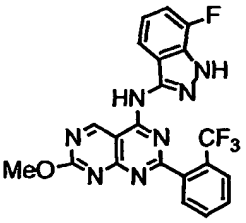

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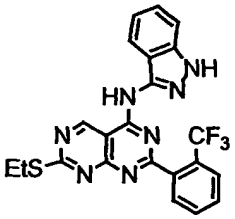

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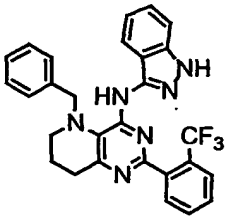

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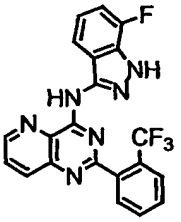

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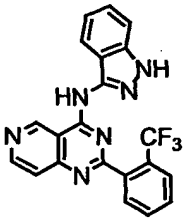

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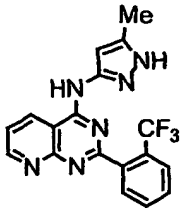

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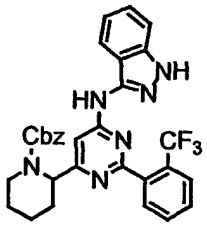

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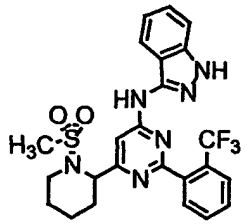

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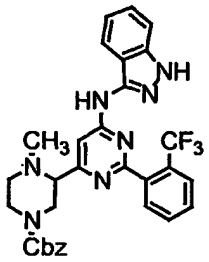

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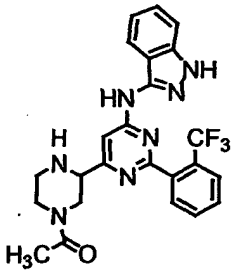

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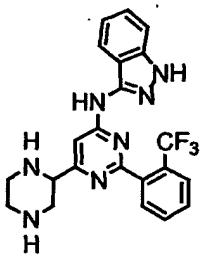

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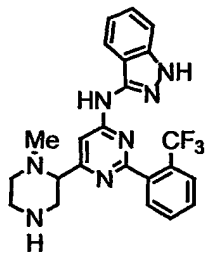

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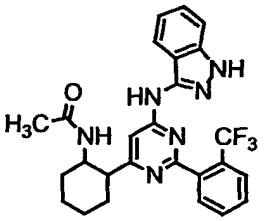

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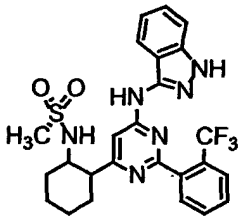

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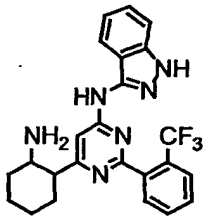

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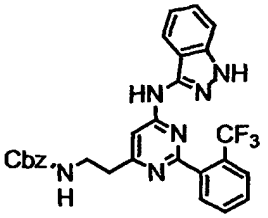

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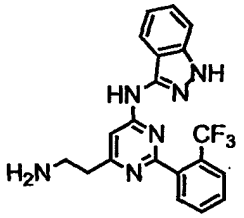

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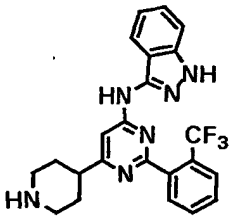

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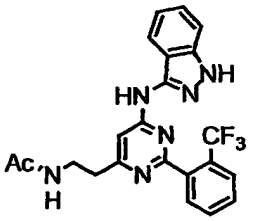

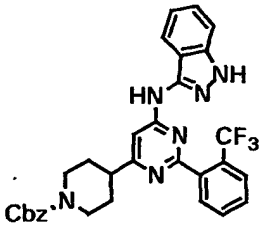

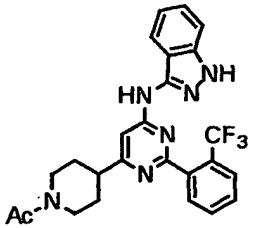

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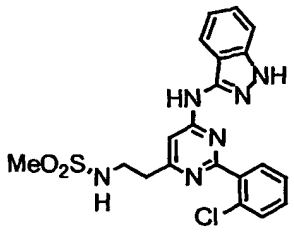

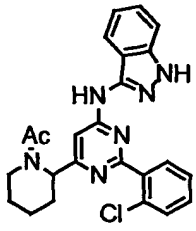

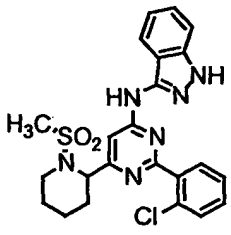

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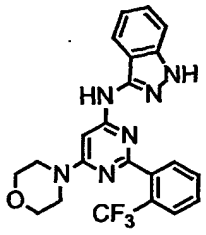

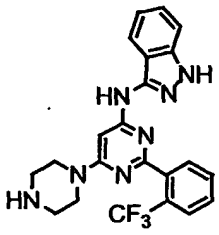

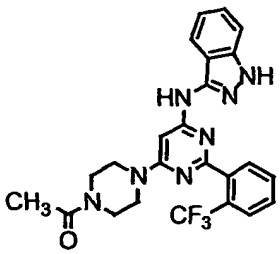

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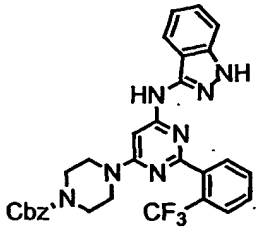

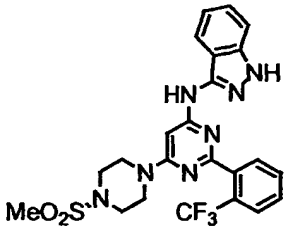

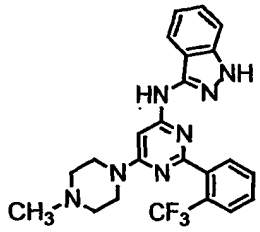

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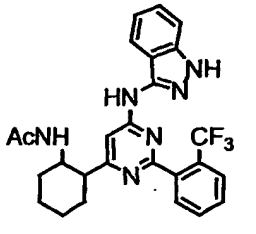

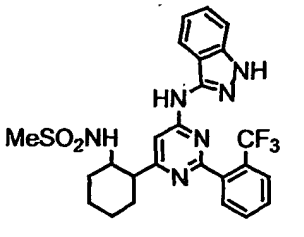

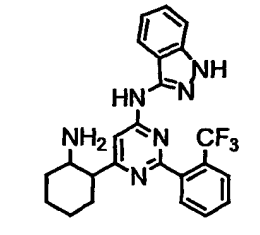

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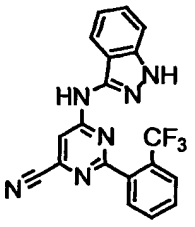

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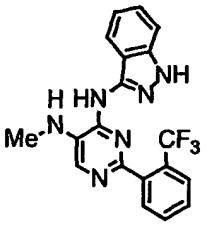

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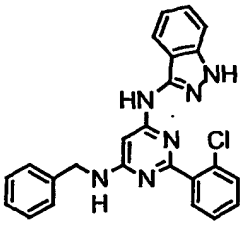

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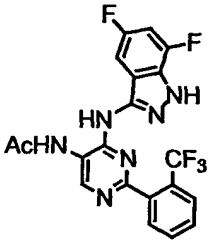

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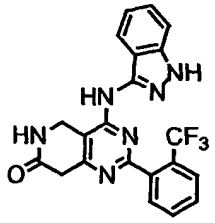

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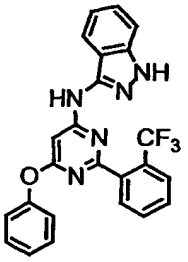

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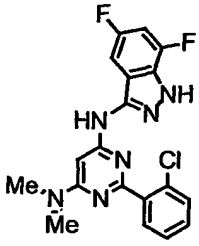

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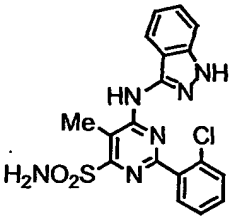

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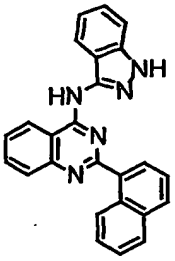

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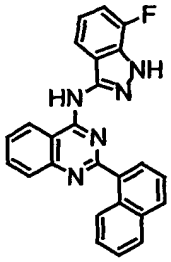

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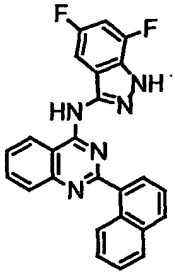

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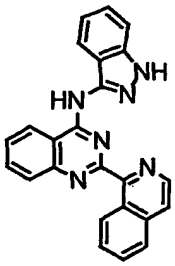

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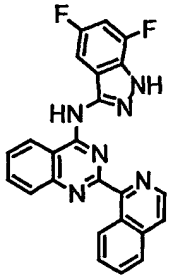

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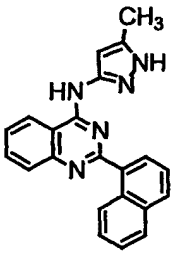

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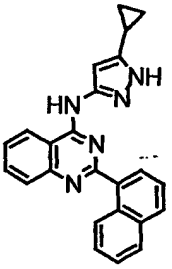

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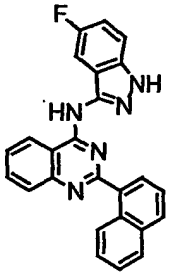

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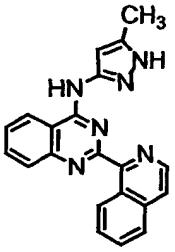

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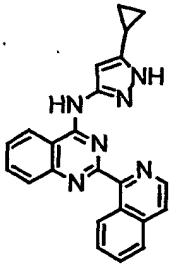

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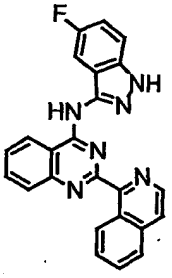

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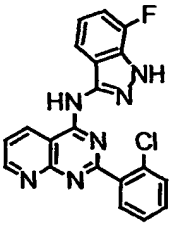

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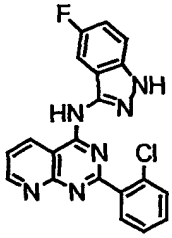

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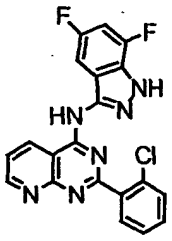

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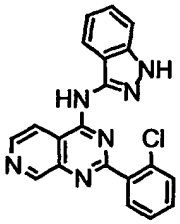

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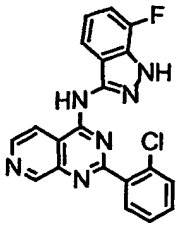

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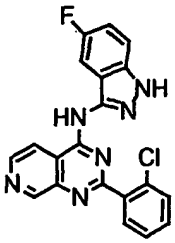

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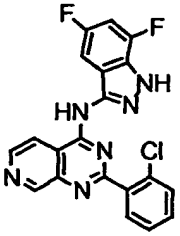

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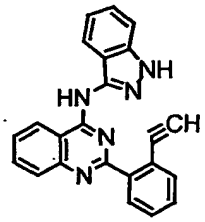

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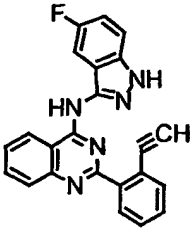

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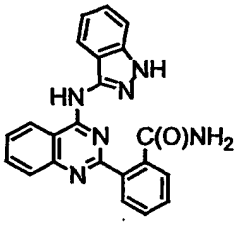

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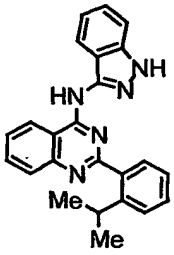

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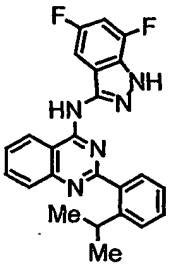

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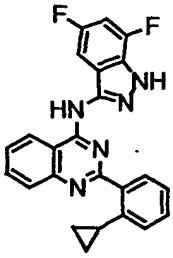

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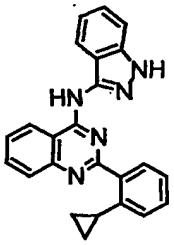

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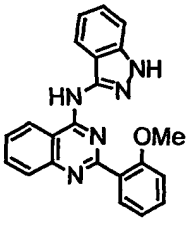

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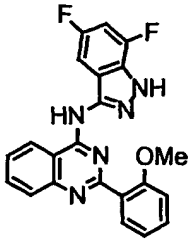

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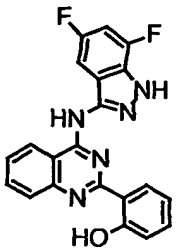

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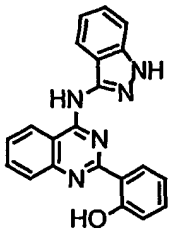

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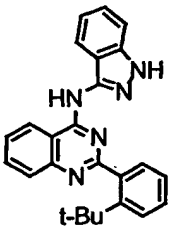

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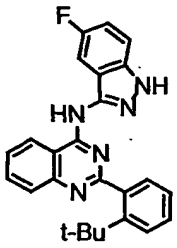

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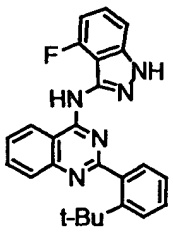

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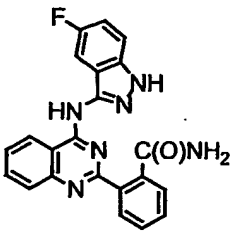

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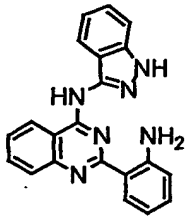

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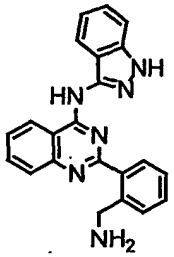

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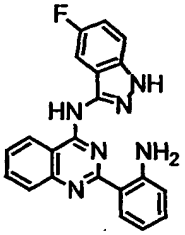

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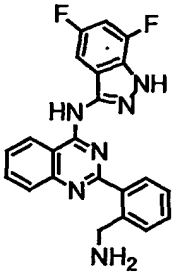

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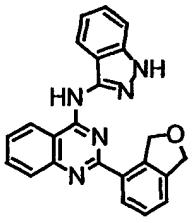

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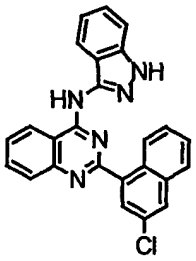

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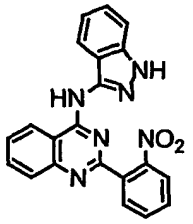

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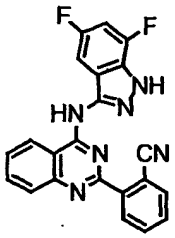

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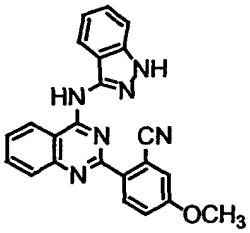

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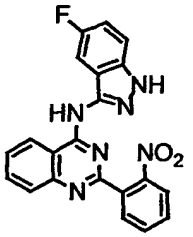

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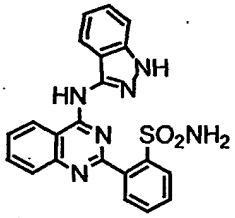

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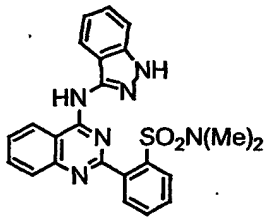

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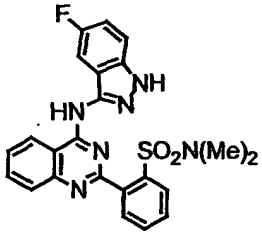

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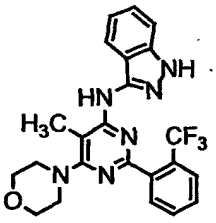

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In another embodiment, this invention provides a composition comprising a compound of formula II and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient,

comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

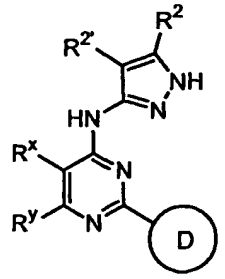
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula II, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula II, as described above.

Another embodiment of this invention relates to compounds of formula III:



III

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^x and R^y are taken together with their intervening atoms to form a fused, benzo ring or a 5-8 membered carbocyclo ring, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or $T-R^3$;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, -T-W-R^6, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, -NO_2, -R^7, or -V-R^6, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

R^3 is selected from -R, -halo, =O, -OR, -C(=O)R, -CO_2R, -COCOR, -$COCH_2$COR, -NO_2, -CN, -S(O)R, -$S(O)_2$R, -SR, -$N(R^4)_2$, -$CON(R^4)_2$, -$SO_2N(R^4)_2$, -OC(=O)R, -$N(R^4)$COR, -$N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), -$N(R^4)N(R^4)_2$, -C=N$N(R^4)_2$, -C=N-OR, -$N(R^4)CON(R^4)_2$, -$N(R^4)SO_2N(R^4)_2$, -$N(R^4)SO_2$R, or -OC(=O)$N(R^4)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from -R^7, -COR^7, -CO_2(optionally substituted C_{1-6} aliphatic), -$CON(R^7)_2$, or -SO_2R^7, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, -C(=O)R, -CO_2R, -COCOR, -NO_2, -CN, -S(O)R, -SO_2R, -SR, -$N(R^4)_2$, -$CON(R^4)_2$, -$SO_2N(R^4)_2$, -OC(=O)R, -$N(R^4)$COR, -$N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), -$N(R^4)N(R^4)_2$, -C=N$N(R^4)_2$, -C=N-OR, -$N(R^4)CON(R^4)_2$, -$N(R^4)SO_2N(R^4)_2$, -$N(R^4)SO_2$R, or -OC(=O)$N(R^4)_2$;

V is -O-, -S-, -SO-, -SO_2-, -$N(R^6)SO_2$-, -$SO_2N(R^6)$-, -$N(R^6)$-, -CO-, -CO_2-, -$N(R^6)$CO-, -$N(R^6)$C(O)O-,

$-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring; and

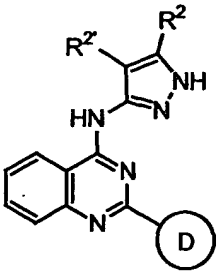
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

Preferred formula III Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula III Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of

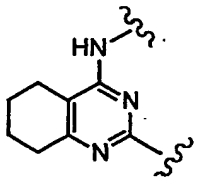
more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred R^5 substituents on Ring D of formula III include halo, oxo, CN, $-NO_2$, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. More preferred R^5 substituents include -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH_2OH, CH_2CH_2OH, pyrrolidinyl, OPh, CF_3, C≡CH, Cl, Br, F, I, NH_2, $C(O)CH_3$, *i*-propyl, *tert*-butyl, SEt, OMe, $N(Me)_2$, methylene dioxy, and ethylene dioxy.

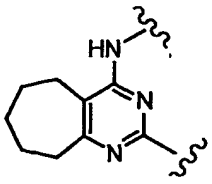
Preferred rings formed when the R^x and R^y groups of formula III are taken together to form a fused ring include a 5-, 6-, or 7-membered unsaturated or partially unsaturated carbocyclo ring, wherein any substitutable carbon on said fused ring is substituted by oxo or $T-R^3$. Examples of preferred bicyclic ring systems are shown below.



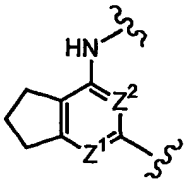
III-A



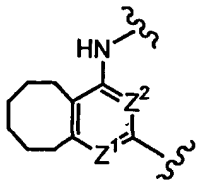
III-B



III-C



III-F



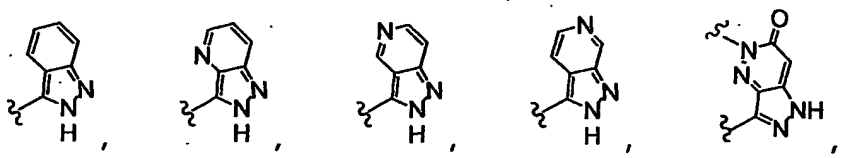
III-I

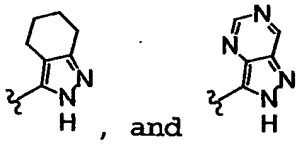
Preferred substituents on the R^x/R^y fused ring of formula III include -R, oxo, halo, -OR, -C(=O)R, $-CO_2R$, -COCOR, $-NO_2$, -CN, -S(O)R, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, wherein R and R^4 are as defined above. More preferred substituents on the R^x/R^y fused ring include halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)carbonyl, (C_{1-6} alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl. Examples of such preferred substituents include methoxy, methyl, isopropyl, methylsulfonyl, cyano, chloro, pyrrolyl, methoxy, ethoxy, ethylamino, acetyl, and acetamido.

Preferred R^2 substituents of formula III include hydrogen, C_{1-4} aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R^2 substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO_2H, CO_2CH_3, CH_2OH, CH_2OCH_3, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_2Ph$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHCOOC(CH_3)_3$, $CONHCH(CH_3)_2$, $CONHCH_2CH=CH_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2Ph$,

CONH(cyclohexyl), $CON(Et)_2$, $CON(CH_3)CH_2Ph$, $CONH(n\text{-}C_3H_7)$, $CON(Et)CH_2CH_2CH_3$, $CONHCH_2CH(CH_3)_2$, $CON(n\text{-}C_3H_7)_2$, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), $CONHCH_3$, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), $CONHCH_2CH_2OH$, $CONH_2$, and CO(piperidin-1-yl).

When the R^2 and $R^{2'}$ groups of formula III are taken together to form a ring, preferred $R^2/R^{2'}$ ring systems containing the pyrazole ring include benzo, pyrido, pyrimido, 3-oxo-2*H*-pyridazino, and a partially unsaturated 6-membered carbocyclo ring. Examples of such preferred $R^2/R^{2'}$ ring systems containing the pyrazole ring include the following:




and

Preferred substituents on the $R^2/R^{2'}$ fused ring of formula III include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

Preferred formula III compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or a 5-7 membered carbocyclo ring; and

(c) $R^{2'}$ is hydrogen or methyl and R^2 is T-W-R^6 or R, wherein W is $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C_{1-6} aliphatic or phenyl, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstitutedbenzo, pyrido, pyrimido, or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula III have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x and R^Y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered carbocyclo ring optionally substituted with -R, oxo, halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic),

$-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, $-C{=}N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$; and

(c) each R^5 is independently selected from halo, oxo, CN, NO_2, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic.

Even more preferred compounds of formula III have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^x and R^y are taken together with their intervening atoms to form a benzo or 6-membered partially unsaturated carbocyclo ring optionally substituted with halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)carbonyl, (C_{1-6} alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

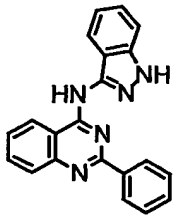
(b) each R^5 is independently selected from -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic; and

(c) $R^{2'}$ is hydrogen and R^2 is selected from $R^{2'}$ is hydrogen or methyl and R^2 is T-W-R^6 or R, wherein W is $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)_2N(R^6)CO-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C_{1-6} aliphatic or phenyl, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl),

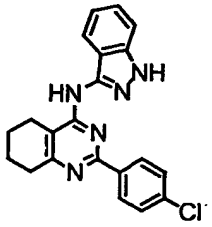
-C(O)NH_2, or -CO(C_{1-4} alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group.

Representative compounds of formula III are set forth in Table 2 below.

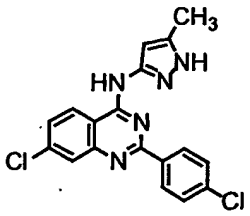
Table 2



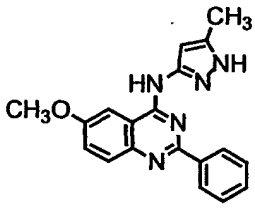
III-1



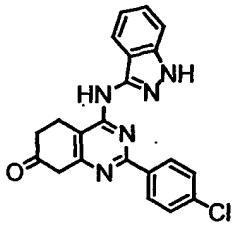
III-2



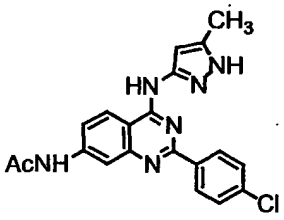
III-3



III-4

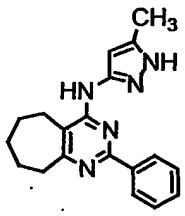


III-5

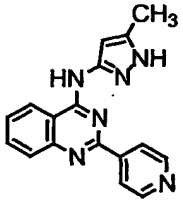


III-6

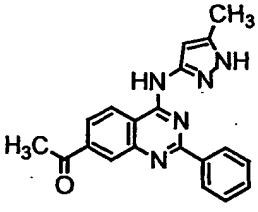
III-7



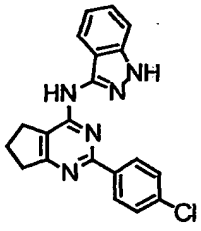
III-8



III-9



III-10



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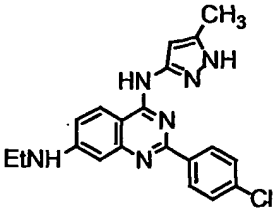

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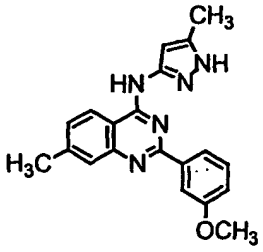

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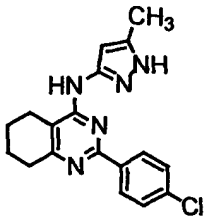

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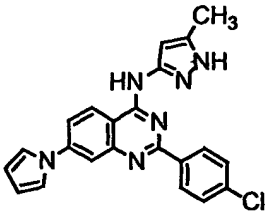

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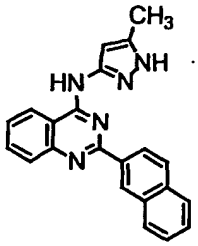

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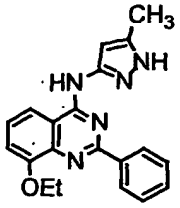

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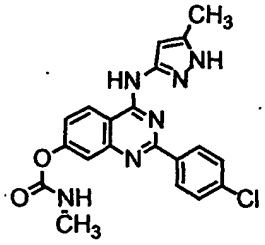

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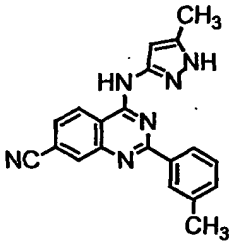

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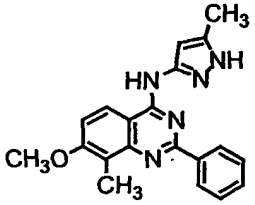

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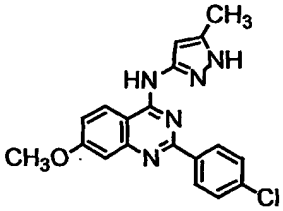

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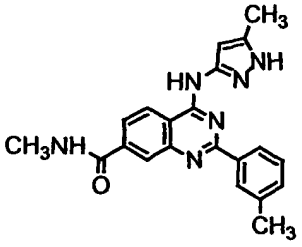

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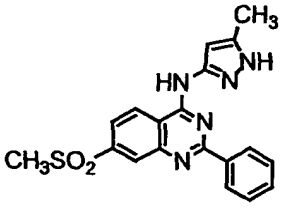

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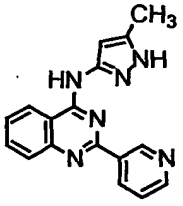

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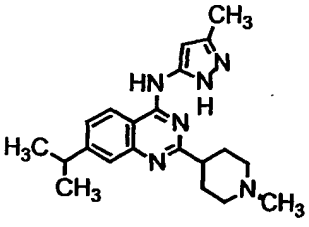

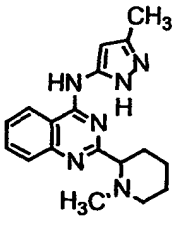

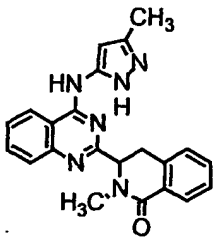

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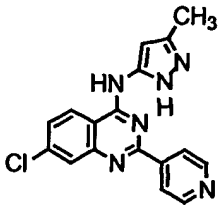
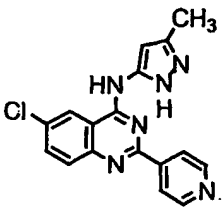
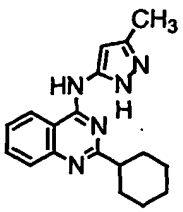

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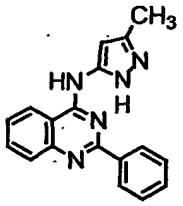
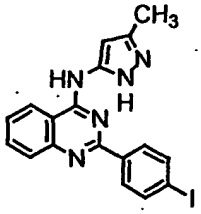
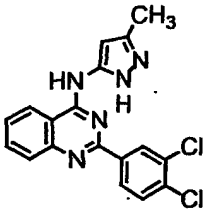

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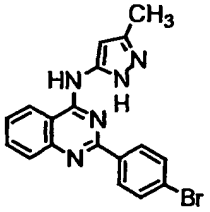
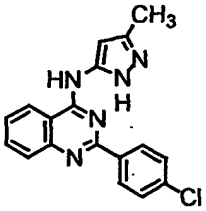
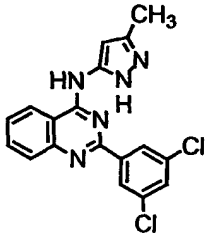

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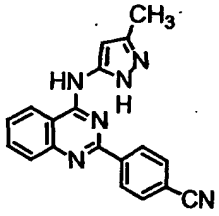
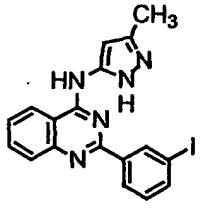
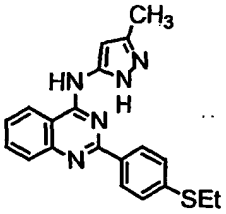

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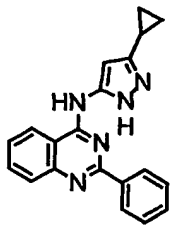

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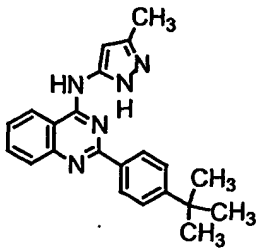

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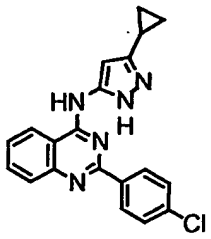

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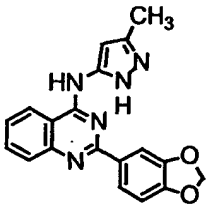

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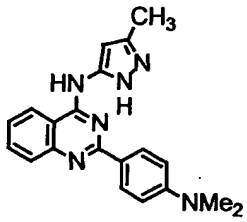

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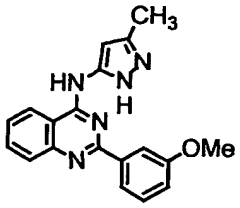

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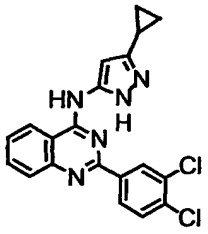

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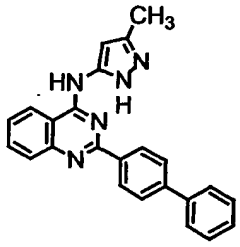

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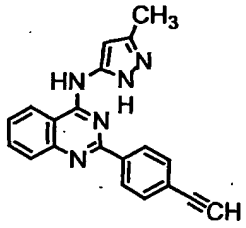

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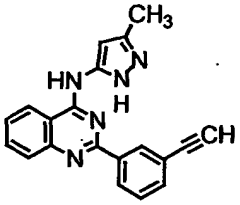

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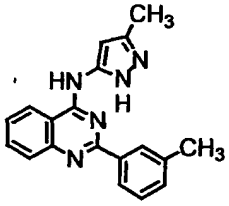

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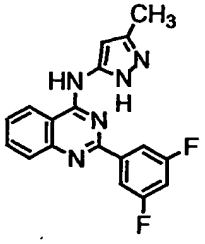

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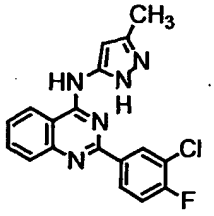

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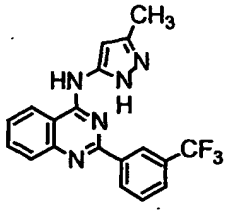

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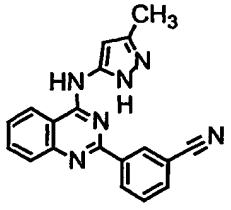

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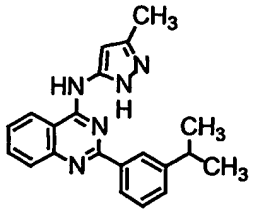

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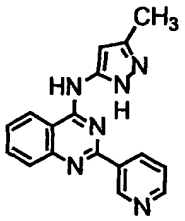

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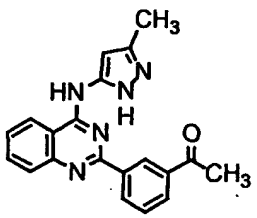

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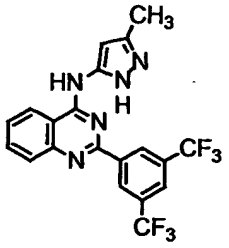

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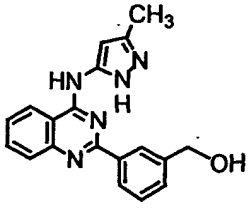

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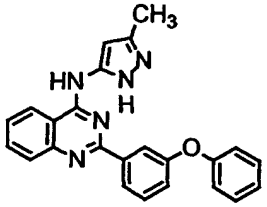

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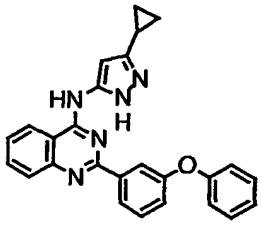

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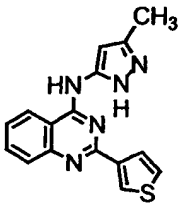

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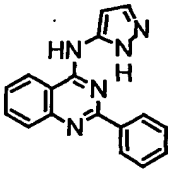

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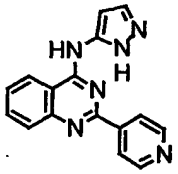

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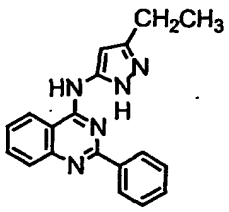

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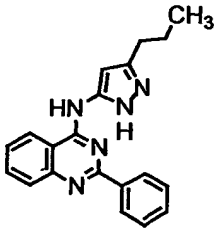

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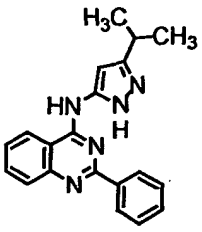

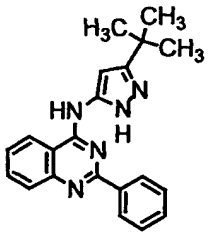

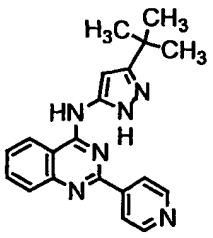

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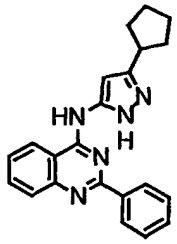

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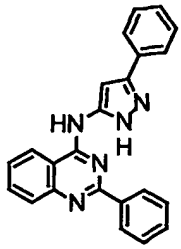

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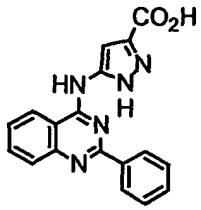

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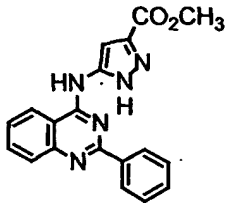

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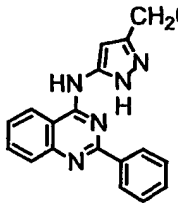

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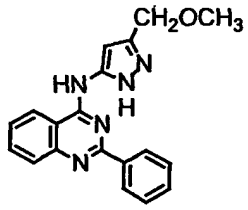

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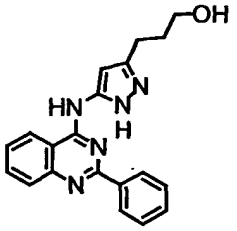

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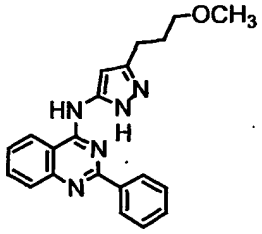

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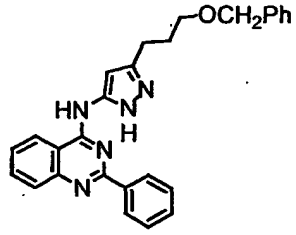

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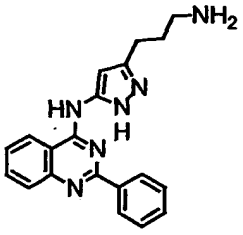

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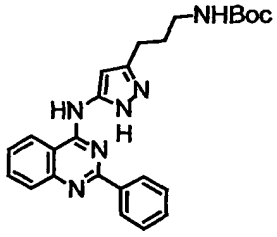

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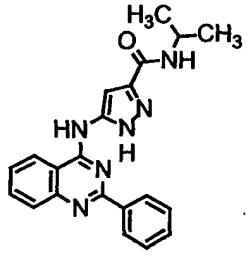

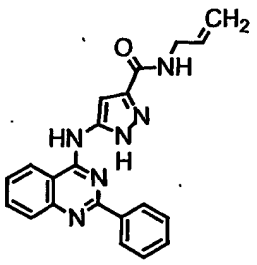

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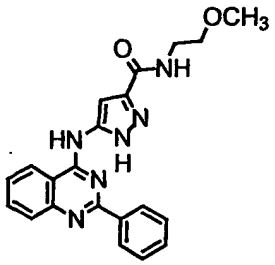

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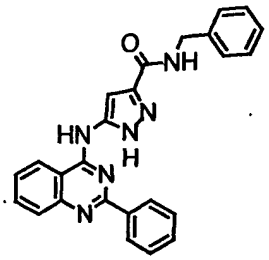

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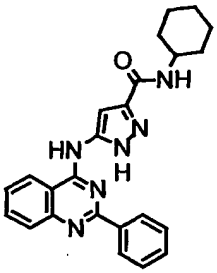

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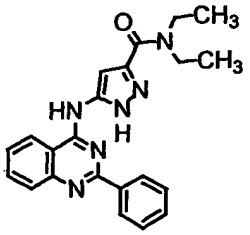

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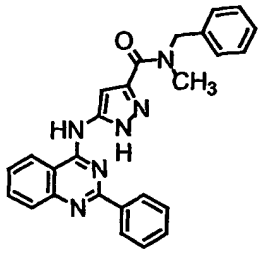

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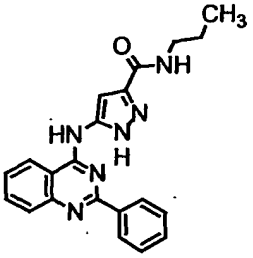

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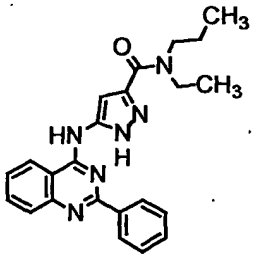

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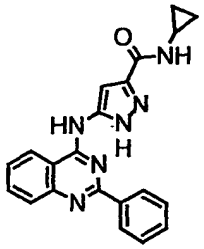

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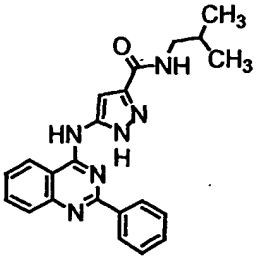

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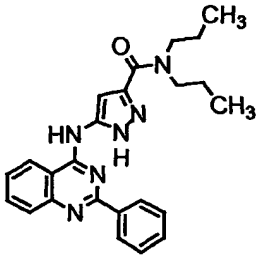

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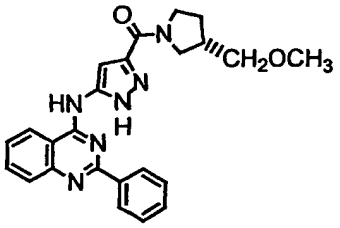

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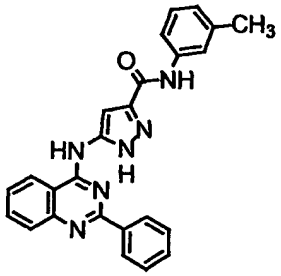

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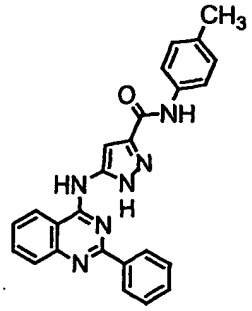

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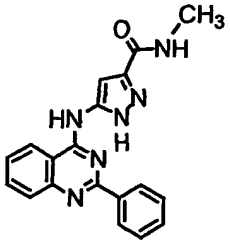

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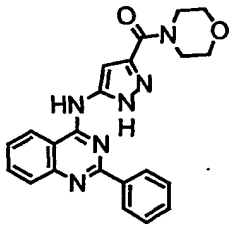

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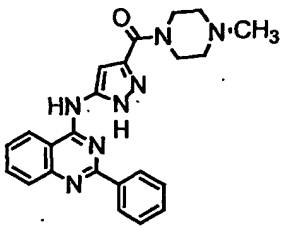

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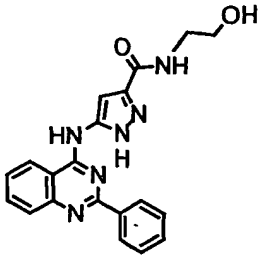

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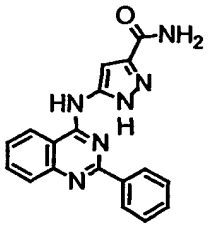

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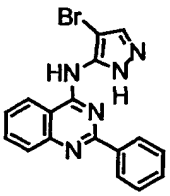

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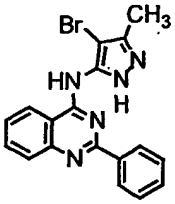

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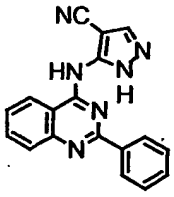

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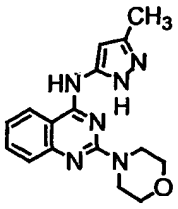

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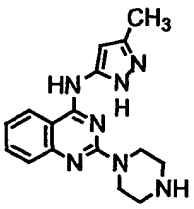

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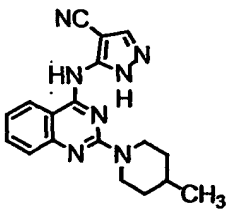

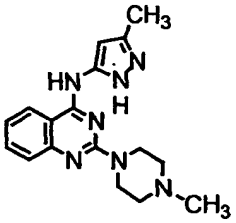

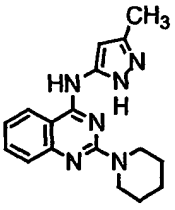

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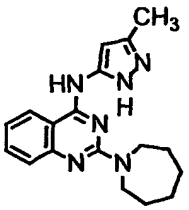
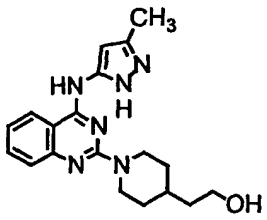
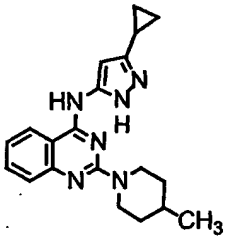

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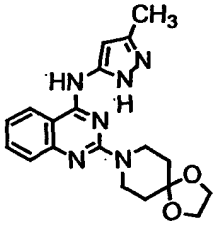
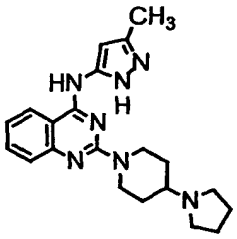
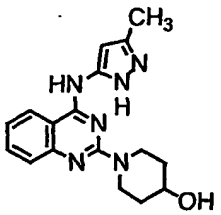

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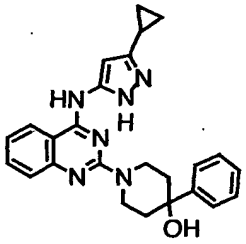
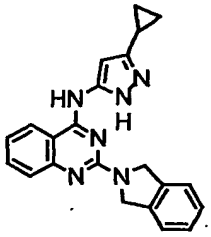
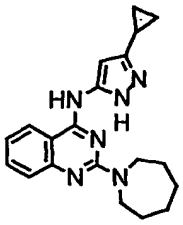
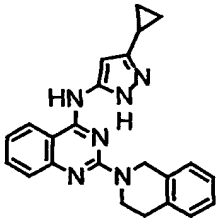
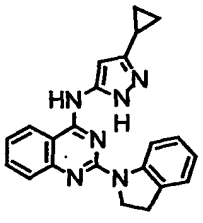
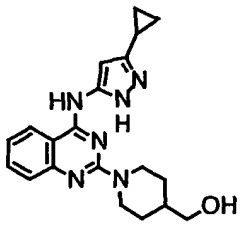




III-115 III-116 III-117

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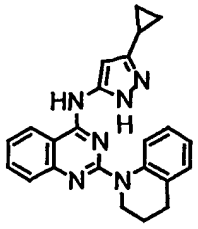

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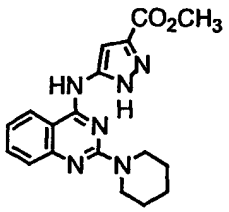

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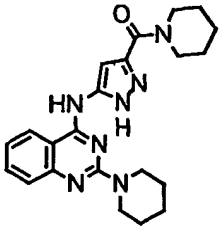

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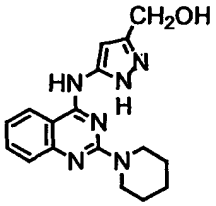
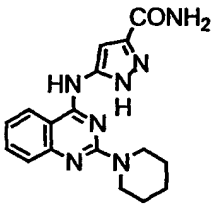


III-124



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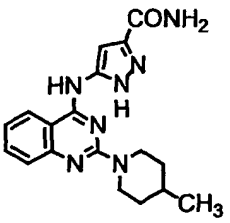

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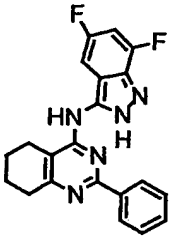

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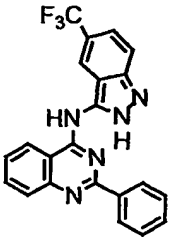

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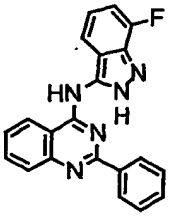

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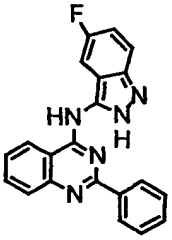

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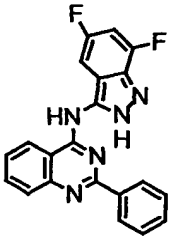

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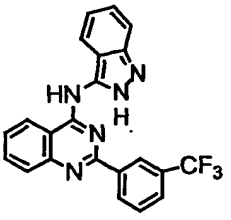

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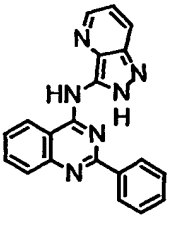

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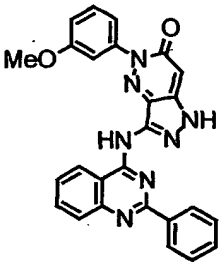

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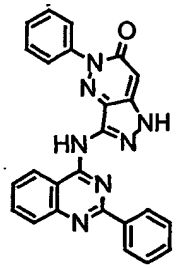

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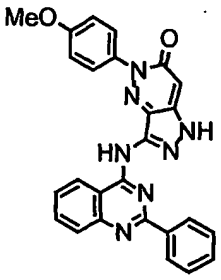

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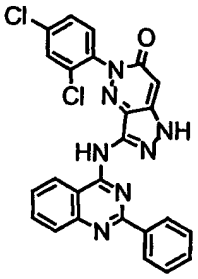

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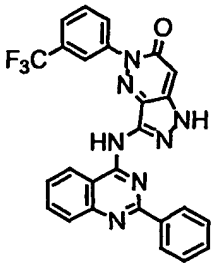

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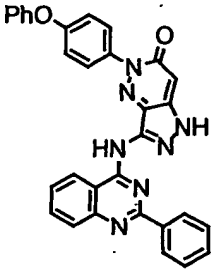

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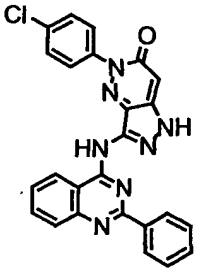

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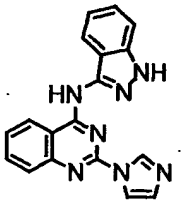

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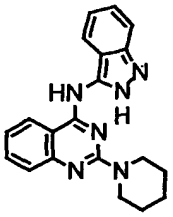
III-142



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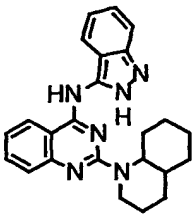

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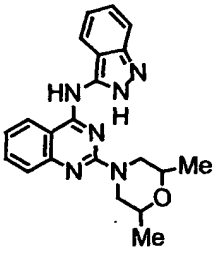
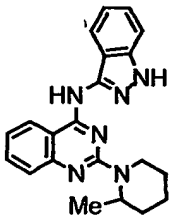


III-145



III-146

In another embodiment, this invention provides a composition comprising a compound of formula III and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition

comprising a compound of formula III. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

One aspect of this invention relates to a method of inhibiting Src activity in a patient,

comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a Src inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for treating hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease.

Another method relates to inhibiting GSK-3, Aurora, CDK-2, or Src activity in a biological sample, which method comprises contacting the biological sample with the GSK-3, Aurora, CDK-2, or Src inhibitor of formula III, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora, CDK-2, or Src.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora, CDK-2, or Src, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula III, as described above.

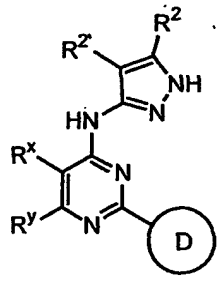
Compounds of formula III, wherein $R^{2'}$ is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system, are also inhibitors of ERK-2 and AKT protein kinases.

Accordingly, another method of this invention relates to a method of inhibiting ERK-2 or AKT activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition

comprising a compound of formula III, wherein $R^{2'}$ is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a ERK-2 or AKT inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III, wherein $R^{2'}$ is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system. This method is especially useful for treating cancer, stroke, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, restenosis, psoriasis, allergic disorders including asthma, inflammation, and neurological disorders.

Another embodiment of this invention relates to compounds of formula IV:



IV

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or

heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^x and R^y are independently selected from $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 1-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring is optionally and independently substituted by $T-R^3$, and any substitutable nitrogen on said ring is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, $-T-W-R^6$, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring containing 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein said fused ring is optionally substituted by up to three groups independently selected from halo, oxo, $-CN$, $-NO_2$, $-R^7$, or $-V-R^6$;

R^3 is selected from -R, -halo, =O, -OR, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-COCH_2COR$, $-NO_2$, $-CN$, $-S(O)R$, $-S(O)_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6}

aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, -S(O)R, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$;

V is -O-, -S-, -SO-, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, -CO-, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring; and

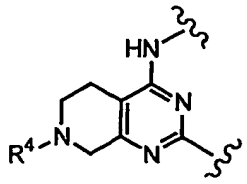
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl ring or heteroaryl.

Preferred formula IV Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. Preferred formula IV Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred Ring D bicyclic rings include naphthyl and isoquinolinyl.

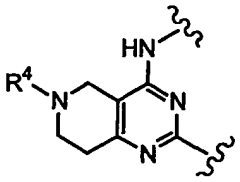
Preferred substituents on Ring D of formula IV include halo, oxo, CN, $-NO_2$, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. More preferred R^5 substituents include -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH_2OH, CH_2CH_2OH, pyrrolidinyl, OPh, CF_3, C≡CH, Cl, Br, F, I, NH_2, $C(O)CH_3$, *i*-propyl, tert-butyl, SEt, OMe, $N(Me)_2$, methylene dioxy, and ethylene dioxy.

When the R^x and R^y groups of formula IV are taken together to form a fused ring, preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 1-2 heteroatoms. This provides a bicyclic ring system containing the pyrimidine

ring. Examples of preferred pyrimidine ring systems of formula IV are the mono- and bicyclic systems shown below.



IV-D



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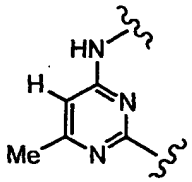

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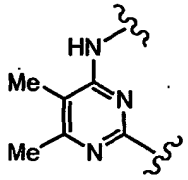

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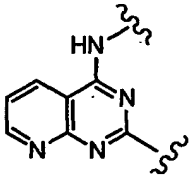

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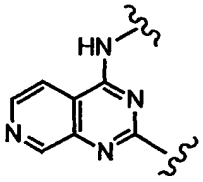
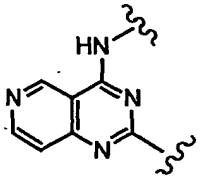
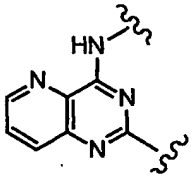


IV-K



IV-L



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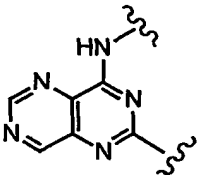

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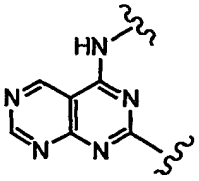
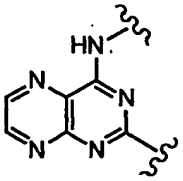
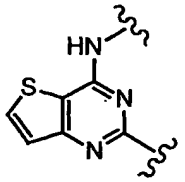


IV-O



IV-P



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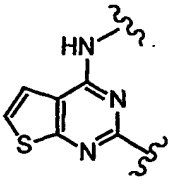

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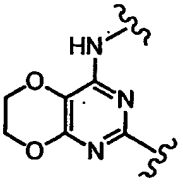

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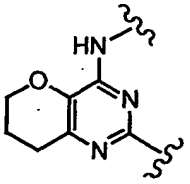

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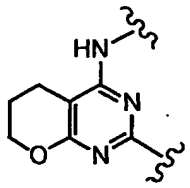

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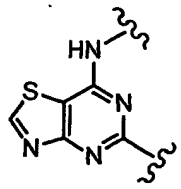

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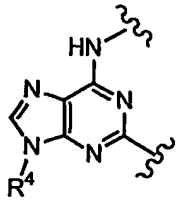

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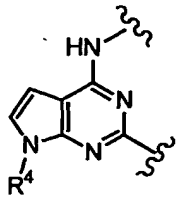

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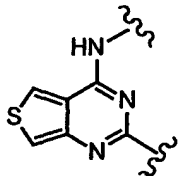

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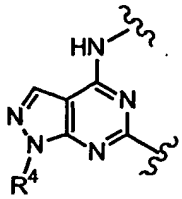

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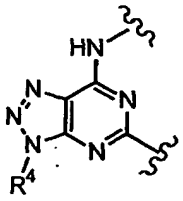

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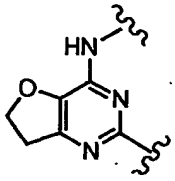

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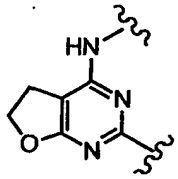

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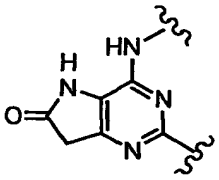


IV-DD

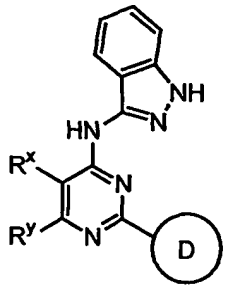
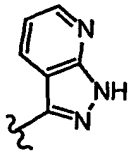
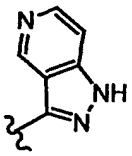
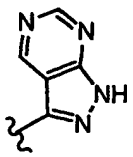
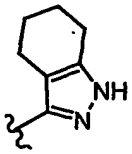
More preferred pyrimidine ring systems of formula IV include IV-E, IV-G, IV-H, IV-J, IV-K, IV-L, IV-M, IV-T, and IV-U.

In the monocyclic pyrimidine ring system of formula IV, preferred R^x groups include hydrogen, amino, nitro, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups include $T-R^3$ wherein T is a valence bond or a methylene, and R^3 is -R,

$-N(R^4)_2$, or -OR. When R^3 is -R or -OR, a preferred R is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y groups include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl, methoxyphenyl, trimethoxyphenyl, or halo-substituted phenyl, and methoxymethyl.

In the bicyclic pyrimidine ring system of formula IV, the ring formed when R^x and R^y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, wherein R and R^4 are as defined above for compounds of formula IV. Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, $-CO_2R$, $-CON(R^4)_2$, -CN, or $-N(R^4)_2$. wherein R is a substituted or unsubstituted C_{1-6} aliphatic group.

The R^2 and $R^{2'}$ groups of formula IV may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula IV compounds having a pyrazole-containing bicyclic ring system:





and


Preferred substituents on the $R^2/R^{2'}$ fused ring of formula IV include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

When the pyrazole ring system of formula IV is monocyclic, preferred R^2 groups include hydrogen, a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group. Examples of such preferred R^2 groups include methyl, t-butyl, $-CH_2OCH_3$, cyclopropyl, furanyl, thienyl, and phenyl. A preferred $R^{2'}$ group is hydrogen.

Preferred formula IV compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x is hydrogen or C_{1-4} aliphatic and R^y is T-R^3, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 1-2 ring heteroatoms; and

(c) $R^{2'}$ is hydrogen or methyl and R^2 is T-W-R^6 or R, wherein W is $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C_{1-6} aliphatic or phenyl, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido, or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula IV have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is -R, $N(R^4)_2$, or -OR, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or partially unsaturated ring having 1-2 ring nitrogens, wherein said ring is optionally substituted with -R, halo, oxo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$; and

(c) each R^5 is independently selected from halo, oxo, CN, NO_2, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic.

Even more preferred compounds of formula IV have one or more, and more preferably all, of the features selected from the group consisting of:

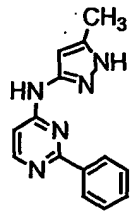
(a) R^x and R^y are taken together with their intervening atoms to form a 6-membered unsaturated or partially unsaturated ring having 1-2 ring nitrogens, optionally substituted with halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)carbonyl, (C_{1-6} alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

(b) each R^5 is independently selected from -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic; and

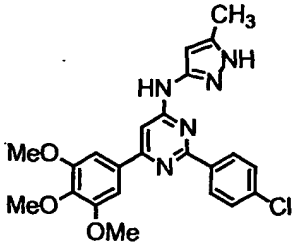
(c) $R^{2'}$ is hydrogen and R^2 is T-W-R^6 or R, wherein W is $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)_2N(R^6)CO-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C_{1-6} aliphatic or phenyl, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, oxo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group.

Representative compounds of formula IV are set forth in Table 3 below.

Table 3.



IV-1



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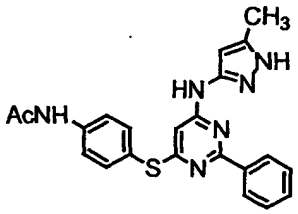

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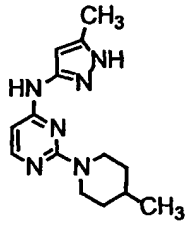

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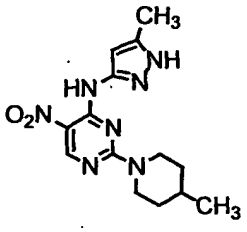

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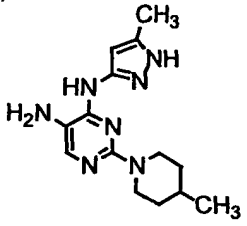

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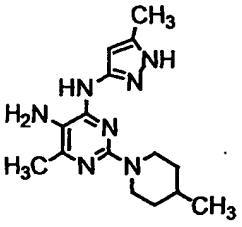

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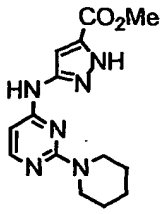

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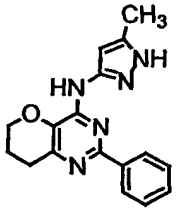

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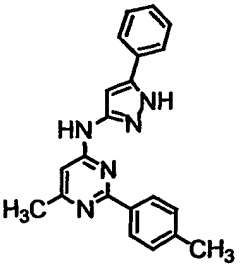

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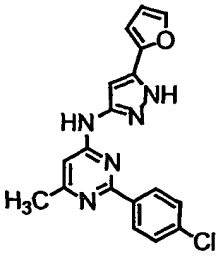

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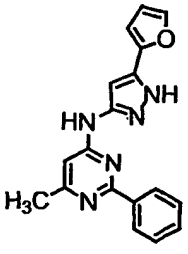

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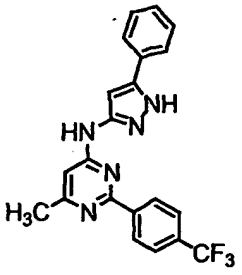

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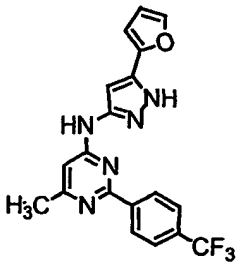

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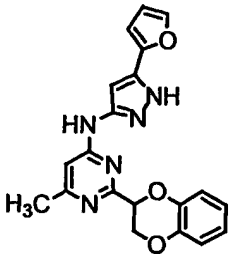

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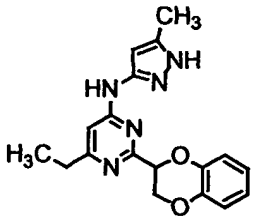

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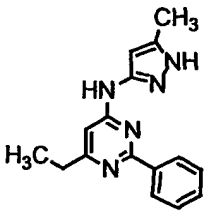

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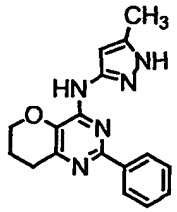

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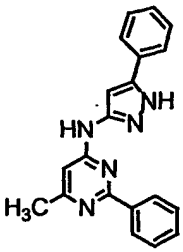

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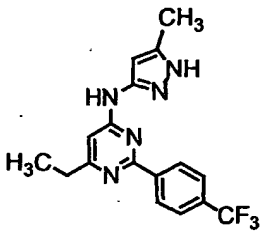
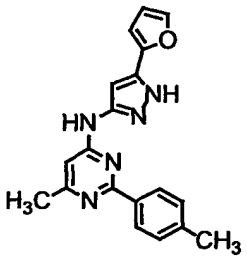


IV-20



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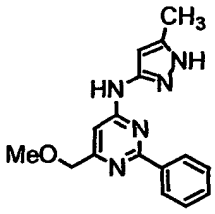

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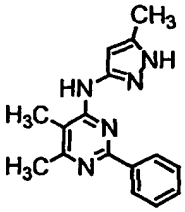

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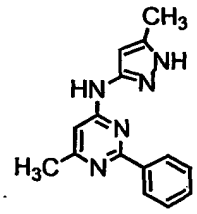

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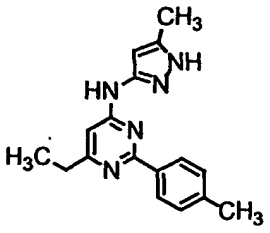

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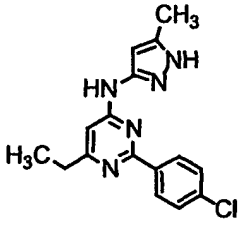

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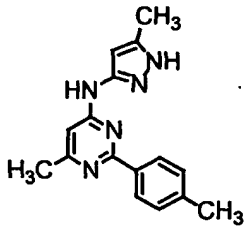
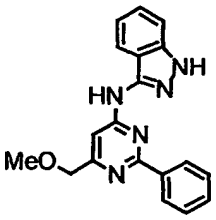


IV-27



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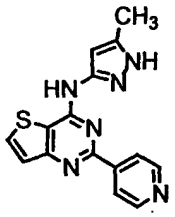

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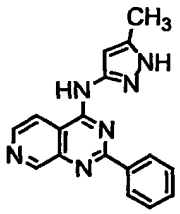

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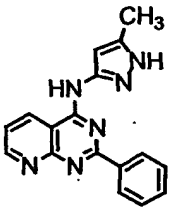

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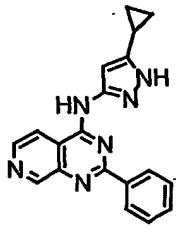

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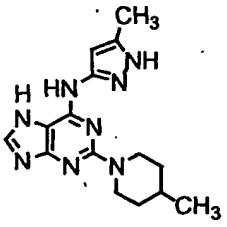


IV-33

In another embodiment, this invention provides a composition comprising a compound of formula IV and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a

therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IV. This method is

especially useful for treating cancer, such as colon, ovarian, and breast cancer.

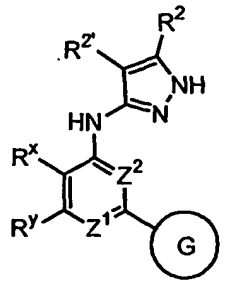
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula IV, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IV, as described above.

Another embodiment of this invention relates to compounds of formula V:



V

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Z^1 is N, CR^a, or CH and Z^2 is N or CH, provided that one of Z^1 and Z^2 is nitrogen;

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or

heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from T-R^3, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R^3, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R^4;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, -T-W-R^6, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or -V-R^6, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

R^3 is selected from -R, -halo, -OR, -C(=O)R, $-CO_2R$, $-COCOR$, $-COCH_2COR$, $-NO_2$, -CN, -S(O)R, $-S(O)_2R$, -SR, $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, -OC(=O)R, $-N(R^7)COR$,

$-N(R^7)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, $-C{=}N{-}OR$, $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, $-C{=}N{-}OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, $-CO-$, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6){=}NN(R^6)-$, $-C(R^6){=}N{-}O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6){=}NN(R^6)-$, $-C(R^6){=}N{-}O-$,

$-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

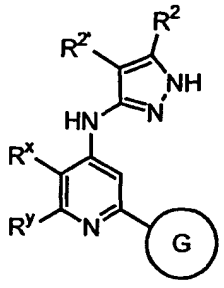
each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

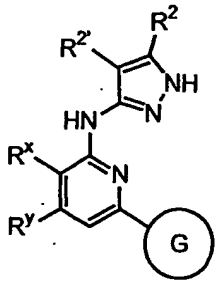
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$; and

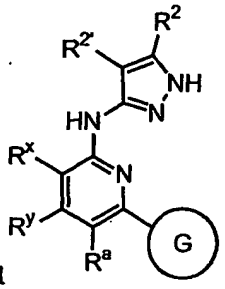
R^a is selected from halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, $-OC(=O)N(R^4)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms.

Compounds of formula V may be represented by specifying Z^1 and Z^2 as shown below:

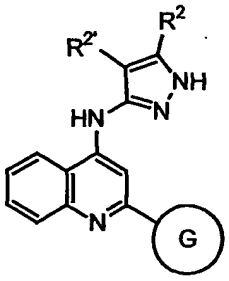

Va

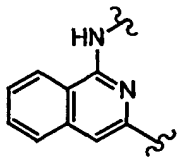

Vb

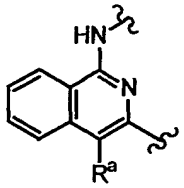
and

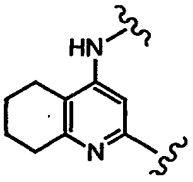

Vc

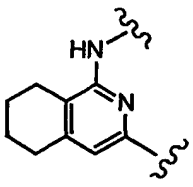
When the R^x and R^y groups of formula V are taken together to form a fused ring, preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 0-2 heteroatoms, wherein said R^x/R^y ring is optionally substituted. This provides a bicyclic ring system containing a pyridine ring. Examples of preferred bicyclic ring systems of formula V are shown below.

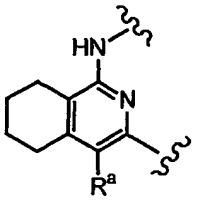

Va-A

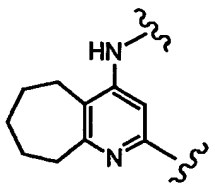

Vb-A


Vc-A

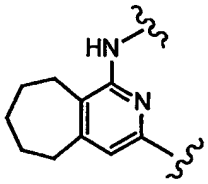

Va-B


Vb-B

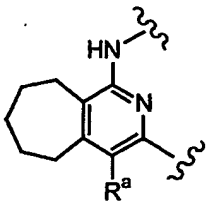

Vc-B



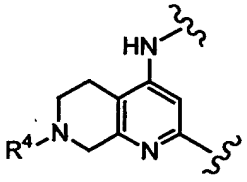
Va-C



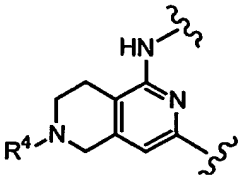
Vb-C



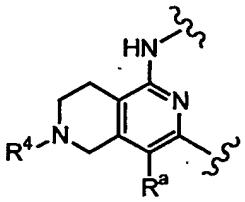
Vc-C



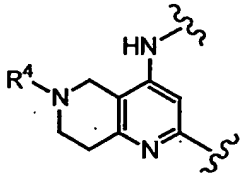
Va-D



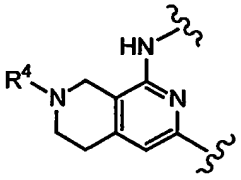
Vb-D



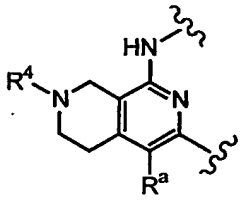
Vc-D



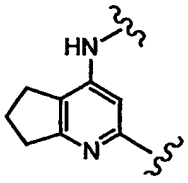
Va-E



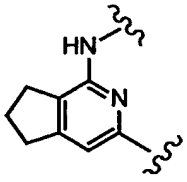
Vb-E



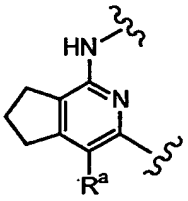
Vc-E



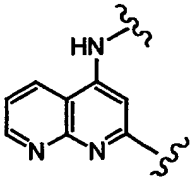
Va-F



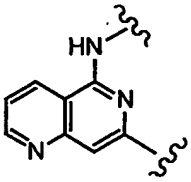
Vb-F



Vc-F



Va-J



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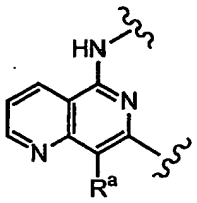

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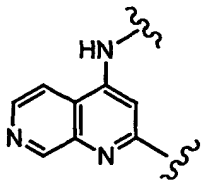
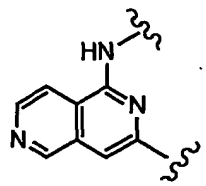


Va-K



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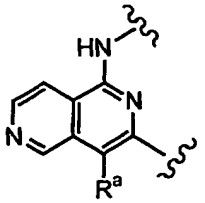
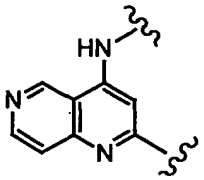


Vc-K



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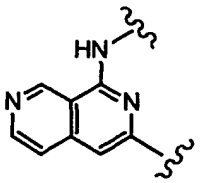

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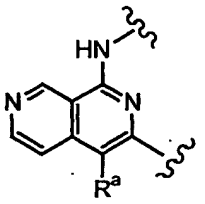
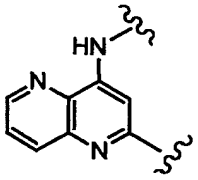
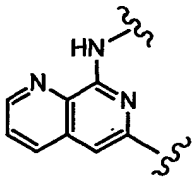


Vc-L



Va-M



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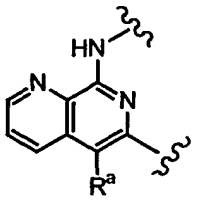
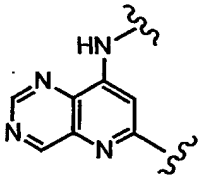


Vc-M



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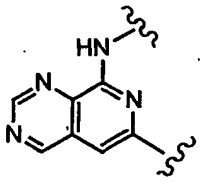

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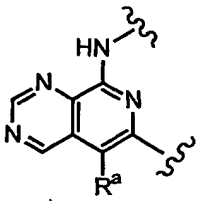
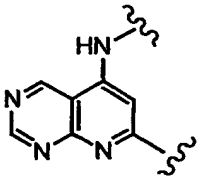
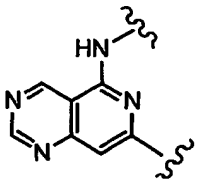


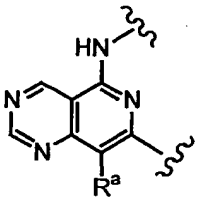
Vc-N



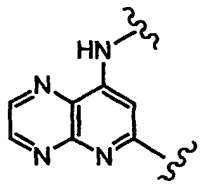
Va-O



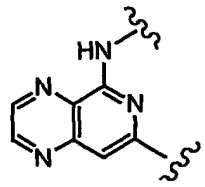
Vb-O



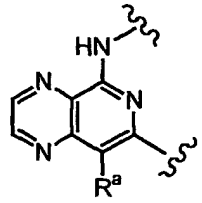
Vc-O



Va-P



Vb-P



Vc-P

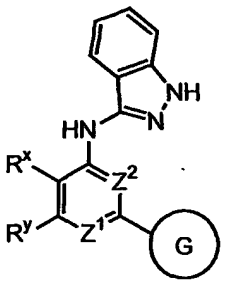
More preferred bicyclic ring systems of formula V include **Va-A**, **Vb-A**, **Vc-A**, **Va-B**, **Vb-B**, **Vc-B**, **Va-D**, **Vb-D**, **Vc-D**, **Va-E**, **Vb-E**, **Vc-E**, **Va-J**, **Vb-J**, **Vc-J**, **Va-K**, **Vb-K**, **Vc-K**, **Va-L**, **Vb-L**, **Vc-L**, **Va-M**, **Vb-M**, and **Vc-M**, most preferably **Va-A**, **Vb-A**, **Vc-A**, **Va-B**, **Vb-B**, and **Vc-B**.

In the monocyclic pyridine ring system of formula V, preferred R^x groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups include $T\text{-}R^3$ wherein T is a valence bond or a methylene, and R^3 is -R, $-N(R^4)_2$, or -OR. When R^3 is -R or -OR, a preferred R is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl, and methoxymethyl.

In the bicyclic ring system of formula V, the ring formed when R^x and R^y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, $-C{=}N\text{-}OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or

$-OC(=O)N(R^4)_2$, wherein R and R^4 are as defined above. Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, $-CO_2R$, $-CON(R^4)_2$, -CN, or $-N(R^4)_2$ wherein R is an optionally substituted C_{1-6} aliphatic group.

The R^2 and $R^{2'}$ groups of formula V may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula V compounds having a pyrazole-containing bicyclic ring system:



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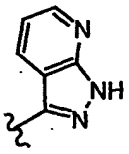

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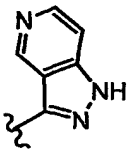

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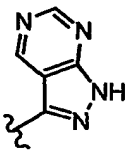

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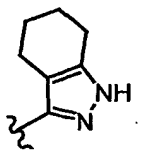

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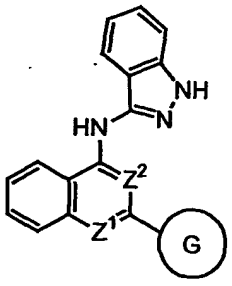
Preferred substituents on the $R^2/R^{2'}$ fused ring of formula V include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

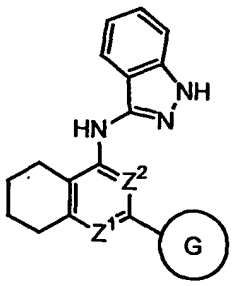
When the pyrazole ring system is monocyclic, preferred R^2 groups include hydrogen, C_{1-4} aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-

heterocyclyl)carbonyl. Examples of such preferred R^2 substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO_2H, CO_2CH_3, CH_2OH, CH_2OCH_3, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_2Ph$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHCOOC(CH_3)_3$, $CONHCH(CH_3)_2$, $CONHCH_2CH=CH_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2Ph$, CONH(cyclohexyl), $CON(Et)_2$, $CON(CH_3)CH_2Ph$, $CONH(n\text{-}C_3H_7)$, $CON(Et)CH_2CH_2CH_3$, $CONHCH_2CH(CH_3)_2$, $CON(n\text{-}C_3H_7)_2$, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), $CONHCH_3$, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), $CONHCH_2CH_2OH$, $CONH_2$, and CO(piperidin-1-yl). A preferred $R^{2'}$ group is hydrogen.

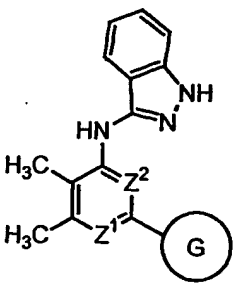
More preferred ring systems of formula V are the following, which may be substituted as described above, wherein R^2 and $R^{2'}$ are taken together with the pyrazole ring to form an optionally substituted indazole ring; and R^x and R^y are each methyl, or R^x and R^y are taken together with the pyridine ring to form an optionally substituted quinoline, isoquinoline, tetrahydroquinoline or tetrahydroisoquinoline ring:



V-Aa



V-Ba



V-Ha

When G is Ring C, preferred formula V Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring.

Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R^1 groups include -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-CF_3$, -Cl, -F, -CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, $-C\equiv CH$, $-C\equiv C-CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-N(CH_3)_2$, $-CO_2CH_3$, $-CONH_2$, $-NHCOCH_3$, $-OC(O)NH_2$, $-NHSO_2CH_3$, and $-OCF_3$.

On Ring C preferred R^5 substituents, when present, include -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, -C(O)R, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, and $-N(R^4)SO_2R$. More preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic). Examples of such preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, -NHMe, $-NMe_2$, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and $-CO_2Et$.

When G is Ring D, preferred formula V Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula V Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, and

naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on Ring D of formula V include one or more of the following: halo, oxo, CN, $-NO_2$, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH_2OH, CH_2CH_2OH, pyrrolidinyl, OPh, CF_3, C≡CH, Cl, Br, F, I, NH_2, $C(O)CH_3$, *i*-propyl, *tert*-butyl, SEt, OMe, $N(Me)_2$, methylene dioxy, and ethylene dioxy.

Preferred formula V compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x is hydrogen or C_{1-4} aliphatic and R^y is T-R^3, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula V have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is -R, $N(R^4)_2$, or -OR, or R^x and R^y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered partially unsaturated carbocyclo ring, said benzo or carbocyclo ring optionally substituted with -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$,

$-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, $-C{=}N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$;

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, -C(O)R, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R$.

Even more preferred compounds of formula V have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form a

benzo ring or a 6-membered partially unsaturated carbocyclo ring optionally substituted with halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)carbonyl, (C_{1-6} alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

(c) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic)$_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

Representative compounds of formula V are set forth in Table 4 below.

Table 4.

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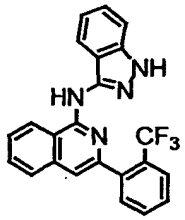

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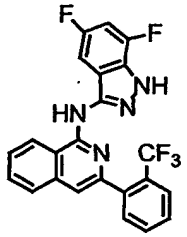

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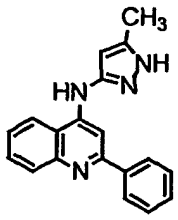

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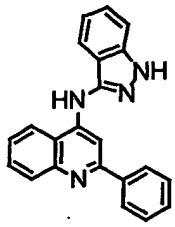

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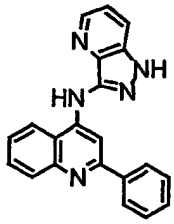

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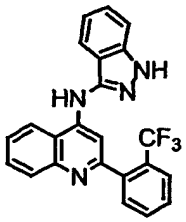

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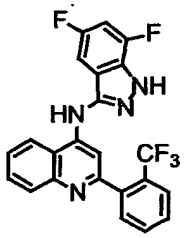

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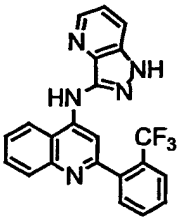

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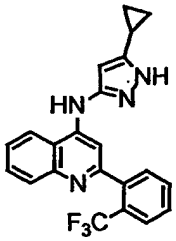

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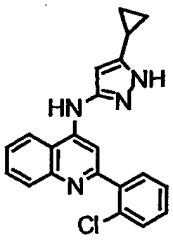

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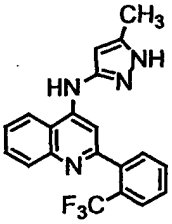

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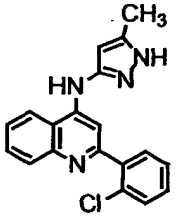

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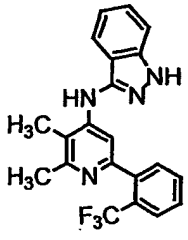

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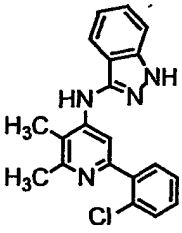

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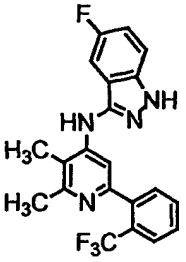
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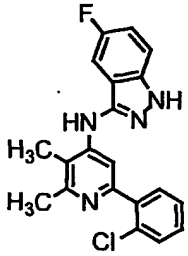
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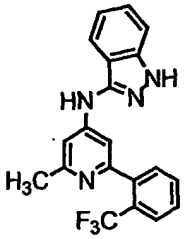
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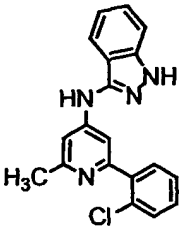
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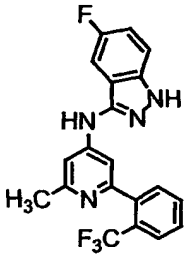
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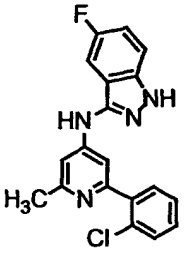
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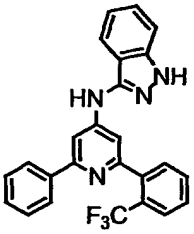
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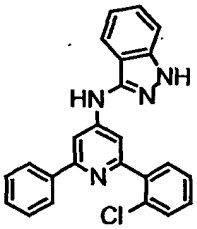
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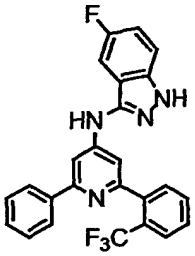
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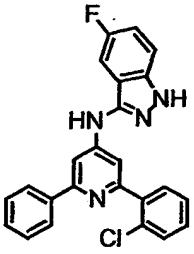
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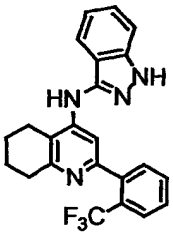
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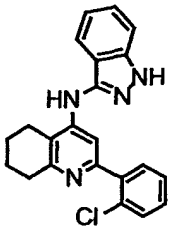
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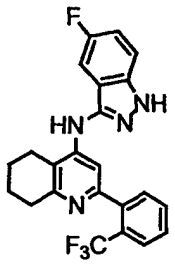
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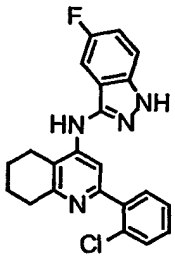
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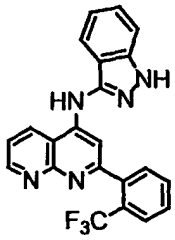
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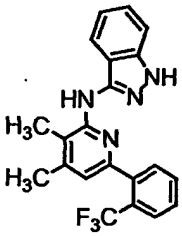
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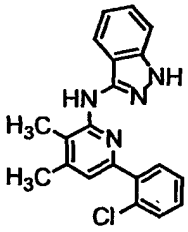
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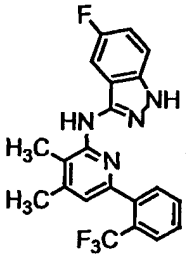
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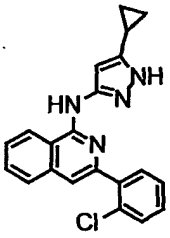
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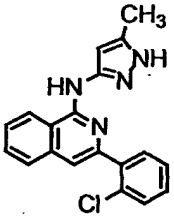
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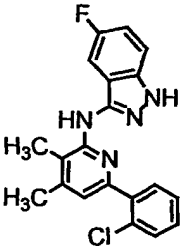
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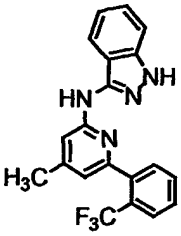
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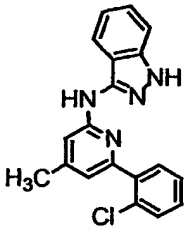
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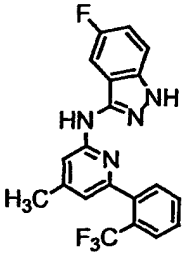
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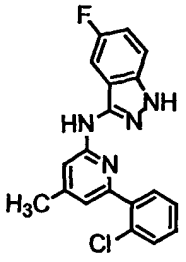
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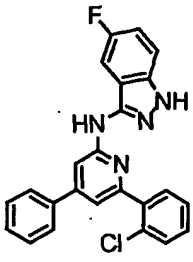
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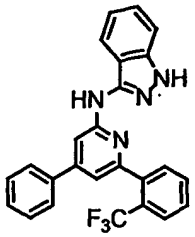
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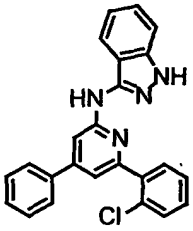
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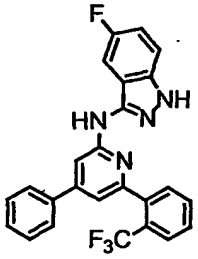
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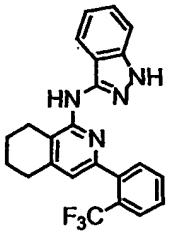
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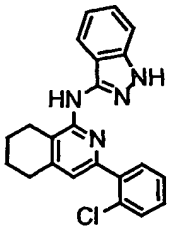
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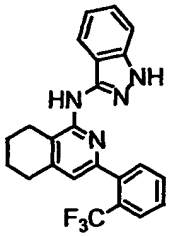
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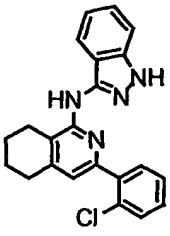
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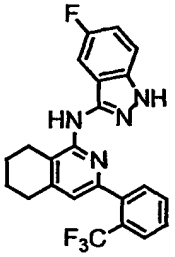
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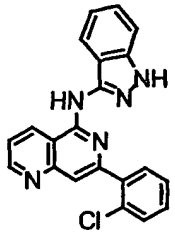

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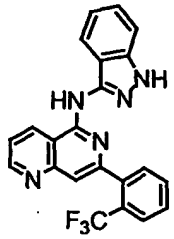

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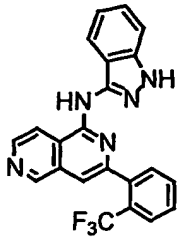

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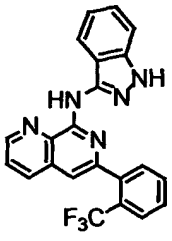

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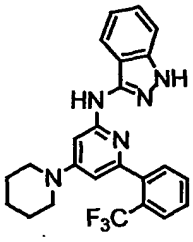

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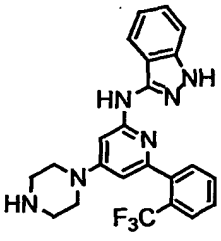

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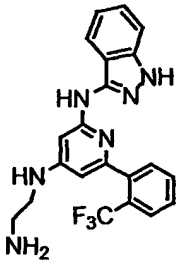

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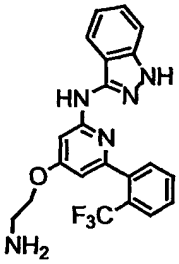

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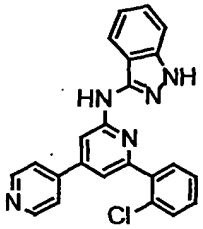

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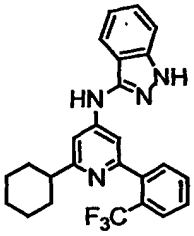

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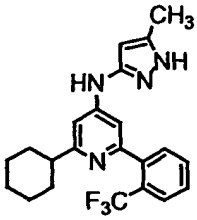

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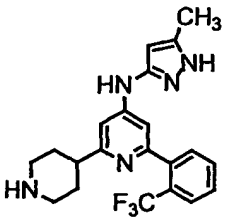

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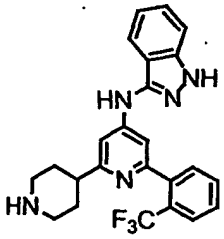

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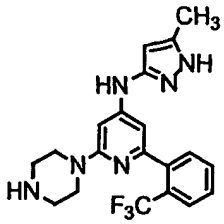

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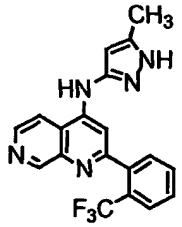
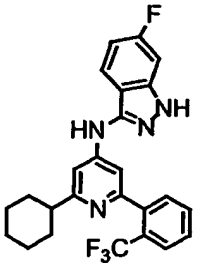
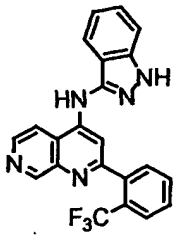


V-66



V-67



V-68

In another embodiment, this invention provides a composition comprising a compound of formula V and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula V.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula

V. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

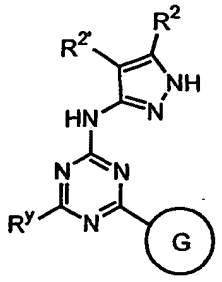
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula V, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula V, as described above.

Another embodiment of this invention relates to compounds of formula VI:



VI

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1

and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^Y is $T\text{-}R^{3'}$;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, $-T\text{-}W\text{-}R^6$, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or $-V\text{-}R^6$, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

$R^{3'}$ is an optionally substituted group selected from C_{1-6} aliphatic, C_{3-10} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C{=}NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and

an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, $-CO-$, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

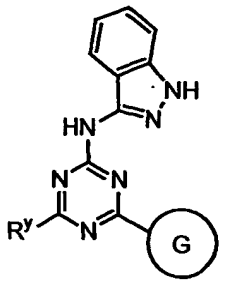
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$.

Preferred R^y groups of formula VI include $T-R^{3'}$ wherein T is a valence bond or a methylene, and $R^{3'}$ is an optionally substituted group selected from C_{1-6} aliphatic,

C_{3-10} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms. A preferred $R^{3'}$ group is an optionally substituted group selected from C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, morpholinyl, cyclopropyl, cyclohexyl, and optionally substituted phenyl such as phenyl or halo-substituted phenyl.

The R^2 and $R^{2'}$ groups of formula VI may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VI compounds having a pyrazole-containing bicyclic ring system:



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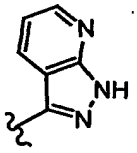

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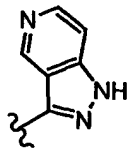

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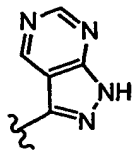

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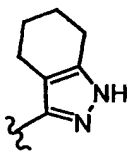

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Preferred substituents on the $R^2/R^{2'}$ fused ring include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

When the pyrazole ring system is monocyclic, preferred R^2 groups of formula VI include hydrogen, C_{1-4} aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R^2 substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO_2H, CO_2CH_3, CH_2OH, CH_2OCH_3, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_2Ph$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHCOOC(CH_3)_3$, $CONHCH(CH_3)_2$, $CONHCH_2CH{=}CH_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2Ph$, CONH(cyclohexyl), $CON(Et)_2$, $CON(CH_3)CH_2Ph$, $CONH(n\text{-}C_3H_7)$, $CON(Et)CH_2CH_2CH_3$, $CONHCH_2CH(CH_3)_2$, $CON(n\text{-}C_3H_7)_2$, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), $CONHCH_3$, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), $CONHCH_2CH_2OH$, $CONH_2$, and CO(piperidin-1-yl). A preferred $R^{2'}$ group is hydrogen.

When G is Ring C, preferred formula VI Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R^1 groups include -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-CF_3$, -Cl, -F, -CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$,

cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH_3, -SO_2CH_3, -SO_2NH_2, -$N(CH_3)_2$, -CO_2CH_3, -$CONH_2$, -$NHCOCH_3$, -$OC(O)NH_2$, -$NHSO_2CH_3$, and -OCF_3.

On Ring C preferred R^5 substituents, when present, include -halo, -CN, -NO_2, -$N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, -C(O)R, -CO_2R, -$CONH(R^4)$, -$N(R^4)COR$, -$SO_2N(R^4)_2$, and -$N(R^4)SO_2R$. More preferred R^5 substituents include -Cl, -F, -CN, -CF_3, -NH_2, -$NH(C_{1-4}$ aliphatic), -$N(C_{1-4}$ aliphatic$)_2$, -$O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and -$CO_2(C_{1-4}$ aliphatic). Examples of such preferred R^5 substituents include -Cl, -F, -CN, -CF_3, -NH_2, -NHMe, -NMe_2, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO_2Et.

When G is Ring D, preferred formula VI Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula VI Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on formula VI Ring D include one or more of the following: halo, oxo, CN, -NO_2, -$N(R^4)_2$, -CO_2R, -$CONH(R^4)$, -$N(R^4)COR$, -$SO_2N(R^4)_2$, -$N(R^4)SO_2R$, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR, -$N(R^4)_2$, -C(O)R, or a substituted or unsubstituted group selected from 5-6

membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH_2OH, CH_2CH_2OH, pyrrolidinyl, OPh, CF_3, C≡CH, Cl, Br, F, I, NH_2, $C(O)CH_3$, *i*-propyl, *tert*-butyl, SEt, OMe, $N(Me)_2$, methylene dioxy, and ethylene dioxy.

Preferred formula VI compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is selected from a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^Y is $T\text{-}R^{3'}$, wherein T is a valence bond or a methylene; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VI have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^Y is $T-R^{3'}$, wherein T is a valence bond or a methylene and $R^{3'}$ is an optionally substituted group selected from C_{1-6} aliphatic, C_{3-6} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, $-C(O)R$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R$.

Even more preferred compounds of formula VI have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^Y is $T-R^{3'}$, wherein T is a valence bond or a methylene and $R^{3'}$ is an optionally substituted group

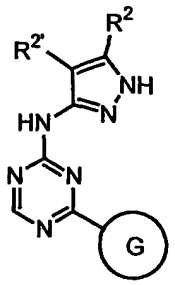
selected from C_{1-4} aliphatic, C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(b) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

(c) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic)$_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

Another embodiment of this invention relates to compounds of formula VIa:



VIa

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or -V-R^6, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$,

$-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, $-CO-$, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

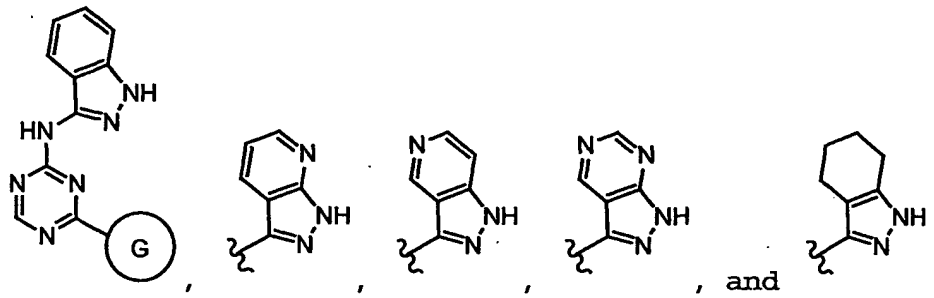
each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$.

Preferred rings formed by the R^2 and $R^{2'}$ groups of formula Via include benzo, pyrido, pyrimido, and a

partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VIa compounds having a pyrazole-containing bicyclic ring system:



Preferred substituents on the $R^2/R^{2'}$ fused ring include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, and $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

When G is Ring C, preferred formula VIa Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R^1 groups include -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-CF_3$, -Cl, -F,

-CN, $-COCH_3$, $-OCH_3$, -OH, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_2CH_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, $-C\equiv C-CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-N(CH_3)_2$, $-CO_2CH_3$, $-CONH_2$, $-NHCOCH_3$, $-OC(O)NH_2$, $-NHSO_2CH_3$, and $-OCF_3$.

On Ring C preferred R^5 substituents, when present, include -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, -C(O)R, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, and $-N(R^4)SO_2R$. More preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic). Examples of such preferred R^5 substituents include -Cl, -F, -CN, $-CF_3$, $-NH_2$, -NHMe, $-NMe_2$, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and $-CO_2Et$.

When G is Ring D, preferred formula VIa Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula VIa Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on the formula Via Ring D include one or more of the following: halo, oxo, CN, $-NO_2$, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR,

$-N(R^4)_2$, $-C(O)R$, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH_2OH, CH_2CH_2OH, pyrrolidinyl, OPh, CF_3, C≡CH, Cl, Br, F, I, NH_2, $C(O)CH_3$, *i*-propyl, *tert*-butyl, SEt, OMe, $N(Me)_2$, methylene dioxy, and ethylene dioxy.

Preferred formula VIa compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring; and

(b) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VIa have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring